T.R.
USKUDAR UNIVERSITY
INSTITUTE OF SCIENCE

DEPARTMENT OF MOLECULAR BIOLOGY AND GENETICS
MASTER'S DEGREE PROGRAM OF MOLECULAR BIOLOGY
MASTER'S DEGREE THESIS

IDENTIFICATION OF TARGET GENES ASSOCIATED WITH SLEEP DISORDERS IN SCHIZOPHRENIA

HALA ALKHANI

Thesis Advisor
Assoc. Prof. Dr. Pınar ÖZ

ISTANBUL-2022

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ABSTRACT

TITLE OF THE THESIS

Sleep disturbance can affect overall health, safety, and quality of life are increase the risk of other problems s including schizophrenia .schizophrenia is a complex neuropsychiatric syndrome with a heterogeneous genetic, neurobiological,and phenotypic profile.

In this study, we will hypothesize. That there is an agentic basis between sleep disorders and schizophrenia, the project focuses on identifying biomarkers to relate sleep-related symptoms in schizophrenia patients and aid with diagnostics, The main *in silico* method utilized in this project was text-mining over the available scientific literature on PubMed and Google Scholar databases. In order to identify the genes that link sleep disorders and schizophrenia, and get the three main result first group Some of the genes that displayed significant symptomatic relationship in schizophrenia through text-mining could not be identified with this method in the literature in relation to any of the symptoms. Second group The genes that could be identified with detailed molecular information in relation to sleep-related symptoms in schizophrenia. Third group Some of the genes that were identified in relation to sleep and schizophrenia did not emerge in the lists for sleep-related symptoms. The first group of genes could be the core of the future, we have to make more research on the relationship between those genes and sleep to aid in future diagnoses found specific treatments.

Keywords: Sleep, Text mining, CoreMine Medical, ShinyGo , Schizophrenia .sleep disorders .

ABSTRACT

TITLE OF THE THESIS

Uyku bozukluğu genel sağlığı, güvenliği ve yaşam kalitesini etkileyebilir, şizofreni de dahil olmak üzere diğer sorunların riskini artırır. Şizofreni heterojen genetik, nörobiyolojik ve fenotipik profile sahip karmaşık bir nöropsikiyatrik sendromdur.Bu çalışmada hipotez kuracağız. Uyku bozuklukları ve şizofreni arasında etken bir temel olduğu, proje şizofreni hastalarında uyku ile ilgili semptomları ilişkilendirmek ve teşhise yardımcı olmak için biyobelirteçlerin belirlenmesine odaklanmaktadır, Bu projede kullanılan temel in silico yöntemi mevcut bilimsel literatür üzerinden metin madenciliğiydi PubMed ve Google Akademik veritabanlarında. Uyku bozuklukları ve şizofreniyi birbirine bağlayan genleri belirlemek ve üç ana sonucu elde etmek için birinci grup Metin madenciliği yoluyla şizofrenide anlamlı semptomatik ilişki sergileyen genlerin bir kısmı literatürde bu yöntemle herhangi bir ilişki ile ilgili olarak tespit edilememiştir. semptomlardan. İkinci grup Şizofrenide uyku ile ilişkili semptomlarla ilgili ayrıntılı moleküler bilgilerle tanımlanabilen genler. Üçüncü grup Uyku ve şizofreni ile ilişkili olarak tanımlanan genlerin bir kısmı uyku ile ilişkili semptomlar listelerinde yer almamıştır. İlk gen grubu geleceğin çekirdeği olabilir, gelecekte teşhis edilen spesifik tedaviye yardımcı olmak için bu genler ve uyku arasındaki ilişki arasında daha fazla araştırma yapmalıyız.

Keywords: Seep , CoreMine Medical, Uyku bozuklukları, Şizofreni, ShinyGo, Text mining

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FORM OF DECLARATION

Herewith I declare, that I obtained all the information and documents in this study within the framework of academic rules, presented all visual, auditory, and written information and results in accordance with scientific ethics, did not falsify the data I used, referred to the sources I used in accordance with scientific norms, that my thesis was original except in the cases cited, produced by me and written in accordance with the Thesis Writing Guide of Uskudar University Institute of Health Sciences.

Date

Student's Name and SURNAME
Signature

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INDEX OF IMAGERY AND ABBREVIATIONS

SD: Sleep Disorders **.**

AI: Acute Insomnia.

CI: Chronic Insomnia.

SCH: Schizophrenia .

ICSD-3 : The International Classification of Sleep Disorders – Third Edition.

DSM-5 : Diagnostic and Statistical Manual of Mental Disorders.

ICD: International Classification of Diseases.

REM: Rapid Eye Movement.

NREM: Non-Rapid Eye Movement.

PS: Primary Sleep.

SS : Secondary Sleep **.**

EEG: Electroencephalogram.

EDS: Excessive Daytime Sleepiness.

CRSD: Circadian Rhythm Sleep Disorders.

CSN: Suprachiasmatic Nuclei.

NDD : Neurodevelopmental Disorders.

GM: Gray Matter.

1. INTRODUCTION

Sleep problems greatly affect all aspects of life in children and adults, with varying severity and symptoms by age. Sleep problems in childhood can lead to various behavioral and mood disorders, such as hyperactivity and poor impulse control (Blunden et al., 2005). These problems can also affect their cognitive and reasoning abilities, memory, and attention (Buckhalt, 2011).Inadequate sleep can also lead to various health conditions, such as an increased risk of cardiovascular and immune system problems (El Shakankiry, 2011). It is currently a debate whether the sleep problems emerging in early childhood are a risk for future neurodevelopmental problems or it is an early symptom with diagnostic value. Nonetheless, it is important to establish the relationship between sleep-related problems in neurodevelopmental and neurodegenerative disorders, both to be able to shed light on its role in the emergence of these disorders and to identify molecular targets for future therapeutical interventions. This thesis project focuses on the identification of target genes that can provide us with the link by utilizing text-mining in the available scientific literature and transcriptomic comparisons.

2. GENERAL INFORMATION

2.1 Sleep Disorders

Sleep Disorders are identified with inability to fall asleep and/or to continue sleeping. They play a negative role in the quality and intensity of sleep and disrupt its duration, often occurring along with other cognitive disorders, (Psychiatry.Org, n.d.) and sometimes emerge as a symptom in different disorders (Smolík, 2019).Sleep disorders can be classified by their etiology : Primary sleep problems are the problems that are not brought on by another physical or mental disease, whereas secondary sleep disorders, such as depression, thyroid issues, stroke, arthritis, or asthma, are caused by other medical conditions (Khoury & Doghramji, 2015).

Sleep disorders are prevalent among all ages in society, where it can be observed among children, adolescents and the elderly :

- Around 25% of all children experience sleep-related problems. These issues are more common in children and adolescents with chronic medical, developmental, and psychiatric disorders (Owens, 2007).
- About 50% of older people experience sleep issues, particularly difficulty in sleeping (Neikrug and Ancoli-Israel, 2010).
- The ratio of adolescents, who met one or more the conditions for a sleep disorder was excessively high, at around 66% (Short et al., 2013).

Different sleep problems have various causes. Sometimes there is no recognized reason ,but mostly other underlying medical conditions trigger sleep-related problems (Karna & Gupta, 2022). All mental illnesses have sleep disturbances as a core component. They may play a significant role in their etiopathogenesis (Smolík, 2019). One of the most common sleep complaints is insomnia. It is a clinical sign that an underlying condition is affecting sleep. Usually, the cause of this condition is a vascular or neurodegenerative disease that affects the central nervous system. Other conditions such as depression and social impairment can also affect sleep.

Some neurological conditions that start or persist while one is sleeping can hinder the onset and/or duration of sleep. These conditions can also affect the quality of sleep. For instance, in fatal familial insomnia, the central nervous system is damaged.

This condition is known to trigger a syndrome that involves the inability to sleep. Besides this, other conditions such as Morvan's disease and delirium tremens can additionally affect sleep. (Provini et al., 2005). Sleep disorders might emerge with a varying spectrum of sleep-related symptoms, most commonly insomnia and hypersomnia. Insomnia The condition known as insomnia is characterized by perceived poor sleep quality that impairs daily performance, Patients with insomnia exhibit increased arousal, difficulty falling asleep, and reported poor sleeping duration and poor sleep quality (Grunstein, 2002). is common and can be acute, or chronic. (Sutton, 2021). Acute insomnia is a sleep continuity disorder, but there is no pathological factor that causes this insomnia, as it might occur 3 times per week, anywhere in the week, during the month (Vargas et al., 2020). According to the three main classifications ICSD-3 , ICD and DSM-5 systems, chronic insomnia was defined based on three criteria : It is (1) characterized by trouble falling asleep and/or staying asleep, (2) linked to daytime effects, frailty, or discomfort, and (3) present despite having enough time to sleep (Vargas et al., 2020).Other type of Insomnia are linked to several diseases, including psychiatric disorders and medical disorders (e.g., chronic pain, dysfunction, and movement disorders). (Billiard & Bentley, 2004).Hypersomnia is a condition that causes excessive sleepiness and can have a detrimental effect on performance and negatively impacts living quality, that could be due to chemistry and circuitry of the brain (Bollu et al., 2018) .

Several studies utilizing neuroimaging techniques reported about changes in specific brain regions in relation with sleep disorders (Desseilles et al., 2008).However, it remains unclear how this information can be used to understand the pathophysiology underlying adult sleep disorders (Desseilles et al., 2008). as a comorbidity With the help of behavioral therapy and medication, individuals can manage their sleep disturbances (Han et al., 2012). On the basis of studies, the classification of types of hypersomnia was identified:

Narcolepsy, idiopathic and recurring hypersomnia, inadequate sleep syndrome, drug- and toxin-dependent somnolence, psychiatric-related hypersomnia, and concurrent hypersomnia are some examples of sleep disorders. For neurological conditions, post-traumatic hypersomnia, infection and hypersomnia, hypersomnia linked to metabolic or endocrine problems, sleep disruptions brought on by sleep apnea syndromes, periodic limb movements while sleeping, and hypersomnia connected with those conditions. (Dauvilliers & Buguet, 2005). Although hypersomnia is a prevalent symptom of psychiatric disorders, there aren't many self-report tests that can accurately describe this sleep problem. (Kaplan et al., 2019).

2.1.1 Classification of sleep disorders

Classification of sleep disorders is important to identify the various types of disorders and to provide a basis for understanding their etiology and treatment. The first systems that were used to classify sleep disorders were based on major symptoms, such as insomnia and excessive sleepiness, and abnormal events that occur during sleep but they were not able to take into account the cause of these disorders (Thorpy, 2012). Although sleep disorders are common in adolescents and children, they are still not entirely understood or treated. There has been a wide range of studies on the prevalence and classification of sleep disorders in children and adolescents, studied among children who usually sleep normally and among children and adolescents with psychosocial and neurodevelopmental diseases (Trosman & Ivanenko, 2021)., which concluded that the symptoms have higher prevalence when there is an underlying condition. The three main complaints of people with sleep disorders are sleep-associated motor phenomena, insomnia, and daytime somnolence. This classification allows for highly accurate diagnoses and helps healthcare providers identify which disorders are most likely to be treated (Rémi et al., 2019). The 2005 version of the International Classification of Sleep Disorder combines the symptoms of insomnia with the pathophysiology of the condition (Thorpy, 2012). The first comprehensive classification of sleep disorders was published in 1990. It was done through the efforts of various international organizations, such as the American Sleep Association and the European Sleep Research Society.(Thorpy, 2001).

2.1.2 Sleep neurochemistry and neural networks

Sleep is a biological process dependent on the circadian rhythm and homeostasis, which work together to organize and control sleep/wakefulness cycles (Stenberg, 2007). Due to homeostatic control, during a period of prolonged wakefulness, sleep will be longer and frequently deeper (Stenberg, 2007). The circadian rhythm is a set of internal biological clocks that are designed to maintain a constant 24-hour cycle. They are triggered by exposure to light and dark cycles (Walker et al., 2020).Sleep is classified into two categories based on behavioral and physiological characteristics. Rapid eye movement (REM) sleep is characterized by rapid eye movements, myasthenia gravis, and asynchronous EEG. Non-REM sleep (NREM) is divided into three phases as N1, N2 and N3. In electroencephalography (EEG), low voltage theta waves were recorded during N1, sleep spindles and K complexes in N2 and delta waves in N3. Delta waves have the lowest frequency and the maximum amplitude (Patel et al., 2022).The transition from wakefulness to sleep is called stage 1. During this period, your body's responses to various stimuli slow down, and your muscles relax. Your brain waves start to slow down from their rhythms of daytime wakefulness.Light sleep is a period of time before you reach the deeper sleep stage. During this time, your body temperature drops, and your eyes stop moving. Your brain activity slows down but is still marked by electrical activity. This type of sleep is more frequent than other sleep stages. Morning awakening is often difficult with non-REM sleep, which is a type of deep sleep that you need to get to feel fresh and ready to start the day. During this period, your breathing and heart rate slow down, which makes it hard to wake up.The first sign of REM sleep is when your eyes move from side to side. This happens about 90 minutes after you have fallen asleep. During this period, your brain's activity begins to resemble that of wakefulness. Your heart rate and blood pressure also increase.

Although most dreams are triggered by rapid eye movement, they can also occur in non-rapid eye movement. As you get older, you sleep less of your time in REM sleep.

Both rapid eye movement (REM) sleep and REM sleep are likely necessary for memory consolidation. (Patel et al., 2022).The internal biological mechanisms are through complex processes that include the regulation of sleep through the homeostatic and circadian rhythms in addition to the participation of many brain structures in wakefulness such as the basal forebrain, posterior and lateral thalamus, pons and islet nucleus. Where acetylcholine and monoamines, glutamate, and hypocretin/orexin are considered important factors in vigilance

Active sleep mechanisms are also found in the preoperative area (frontal hypothalamus).

Gamma-aminobutyric acid and several peptide factors, including cytokines, growth hormone-releasing hormone, and prolactin, are associated with the promotion of sleep. Adenosine is an important homeostatic sleep factor that acts in primary presynaptic forebrain regions through receptors, and activates prolonged awakening by nitric oxidestimulated complex in the basal forebrain which by depletion of energy leads to the release of adenosine and restorative sleep.(Holst & Landolt, 2018). The dominant inhibitory neurotransmitter in the CNS is GABA.The neurotransmitter gamma-aminobutyric acid is produced by certain groupings of basal forebrain neurons and groups of neurons in the hypothalamus. These GABA neurons' projections prevent cells involved in wakefulness from activating.(Gottesmann, 2002). Despite the plethora of data indicating that various brain regions such as the “primary forebrain, tuberosity mammary nucleus, lateral hypothalamus, and nucleus accumbens” are involved in adenosine control of sleep, entire neural circuits in the brain are involved in sleep-promoting effects. for adenosine. unclear (Lazarus et al., 2019).

2.1.3 Cognitive symptoms of sleep disorders

All mental illnesses have sleep disturbances as an essential component, which may play an important role in their etiology (Smolke, 2019). It is generally known that sleep is essential for brain development and the development of important cognitive abilities including memory encoding and learning (Miller et al., 2014).

Insomnia is the most common symptom of sleep disorders in adults according to clinics and the general population (Roth and Royers, 2003), and is characterized as one of the most prevalent sleep disorders, as it divides its neurocognitive which in turn includes

Attention**,** It must be mentioned that attention divided to:

- Focused
- Sustained
- Shifting is

Memory : must be mentioned that memory divided to:

- Working
- Implicit/Explicit

Executive Function : must be mentioned that Executive Function divided to:

- Cognitive Flexibility ,
- Inhibitory Control.(Brownlow et al., 2020).

In a previous study, the role of sleep deprivation in specific cognitive systems was clarified, for example, it was observed that logical and rule-based reasoning and decision-making are not so much affected by sleep deprivation, but, on the contrary, the effect of sleep deprivation in the more creative and innovative aspects (Killgore, 2010), as noted at the end of the study the role of emotion, as recent studies indicate that sleep deprivation has an effect on cognitive systems that depend on emotional data (Kilgore, 2010).

Adolescence brings about significant changes in sleep physiology and circadian rhythms, particularly SWS, which may affect how the body reacts to sleep deprivation.

(Campbell et al., 2007).

2.2 Sleep Disorders and Neurodevelopment

The development of the human brain is one of the most complex and most organized processes, as it consists of many functional areas, circulatory systems and different types of cells. The development process takes place at the structural and functional levels. It also largely depends on healthy genes and normal gene expression, because any defect in them may lead to mutations that prevent gene expression or contribute to the formation of neurological and psychological conditions such as autism or schizophrenia (Tebbenkamp et al., 2014).People with neurodevelopmental disorders (NDDs) have sleep complaints related to insomnia and hypersomnia (Robinson-Shelton and Malow, 2016). For normal postnatal brain development, getting enough sleep is crucial, because it has a role in promoting cognitive and social development. Prolonged sleep deprivation may cause psychological diseases such as stress, depression and cognitive impairment, where sleep disturbances are a symptom of many mental health disorders. The emergence of sleep disorders seems to be a two-way relationship, where sleep can be a cause and also a result.

Several studies compared the effects of sleep deprivation early in life with behavioral disturbances later (Alrousan et al., 2022).

2.2.1 Developmental Problems Leading to Sleep Disorders

Sleep Disorders associated with developmental disorders can be classified into three groups:

1. The first group is physiological sleep disorders, such as rapid eye movement disorders.

2. The second group is sleep disorders that are more prevalent in certain groups of children, and are associated with their underlying condition, such as muscle weakness.

3. The third group is sleep problems of non-specific origin, such as difficulty falling asleep, and waking at night. (Wiggs, 2001). Several types of research have shown the relationship between poor cognitive performance and short sleep, long sleep, and sleep difficulties. (Kronholm et al., 2009). On the other hand, sleep disturbances may be caused by developmental delays and weakness. Compared to normally growing children, young children with developmental delays have sleep disturbances at a greater rate; The most common forms are difficulty falling asleep or staying asleep and breathing while asleep. (Bonock and Grant, 2012). Several studies have compared the effects of sleep deprivation early in life on behavioral disorders later on. Al-Rusan et al., 2022).It is widely known that sleep is essential for brain development as well as for the growth of key cognitive processes including memory and learning. (Li et al., 2007).It is known that prolonged sleep deprivation during the day is associated with decreased activity of the cortical network. This activity is related to the organization of higher cognitive processes such as planning and decision-making. It may also be that lack of sleep leads to the employment of a specific attention strategy. Although the exact mechanisms by which sleep and cognition are linked are still not well understood, it is known that certain areas of the brain are more susceptible to sleep deprivation. These include areas of the brain that are involved in higher cognitive functions. M. A. Miller, H Wright, J Hough, n.d.),

2.2.2 Neurodevelopmental Impact of Sleep Disorders

Neurodevelopmental Disorder (NDD) refers to a broad group of illnesses whose beginning coincides with ongoing stages of maturation and development (Ehninger et al., 2008). During development, the brain is exposed to sensitive periods. Changes in genetic and environmental factors can affect the proper development greatly in these periods and create an impediment, affecting cognition and behavior in adulthood (Suri et al., 2015).

People with developmental or intellectual disabilities (DD or ID) have sleep issues more frequently than people in the general community (BARTLETT et al., 1985).Symptoms of NDDs include impaired intelligence, communication disorders, and cognitive impairment. Some of the more common NDDs include autism spectrum disorder, bipolar disorder, fragile X syndrome, Rett syndrome, intellectual disability and Tourette's syndrome

(Van Lo and Martins, 2007). Schizophrenia is also considered among NDDs, even though there is a debate on its classification. Sleep disorders are more common among children with NDDs than among healthy children, and sleep disturbances in this population are caused by environmental, neurological, and biological interactions. (Robinson Shelton & Mallo, 2015).

2.3 Schizophrenia and Sleep

Schizophrenia is a complex psychiatric disorder that affects multiple aspects of human behavior and cognitive functioning. It usually begins in adolescence or early adulthood. It has a deteriorating course and is characterized by significant abnormalities in the subcortical and cortical regions (Danielyan & Nasrallah, 2009).While positive symptoms “delusions and hallucinations”, negative symptoms “anhedonia, social withdrawal” (Kaskie et al., 2017).Numerous studies have demonstrated in psychological and neurological tests that schizophrenic patients have sleep disturbances and circadian rhythms were the poorest performance, and other studies confirm that psychotic symptoms can lead to sleep disturbances specifically. Kaskie et al., 2017). Depending on the severity of psychotic symptomatology, 30-80% of schizophrenia patients experience disturbed sleep. (Cohrs, 2008). In a previous study, it was shown that schizophrenia may be a disorder in brain development or a disorder in the early development of the brain (around or before birth) (Keshavan et al., 2020).

2.3.1 Etiology of Schizophrenia

The etiology of schizophrenia is complicated because it is multifactorial and displays an interplay between genetic vulnerability and environmental contributors. For the environmental risk factors, childhood trauma, migration, social isolation, urbanicity, and substance abuse, alone and in combination, can be given as examples (Stilo and

Murray, 2019). Schizophrenia is known to include structural abnormalities of the brain, including reduced total gray matter (GM) volume in the cortex, hippocampus, and amygdala (REF). The loss of cortical GM seems to proceed with time (Gogtay,2008). One of the most important factors that could contribute to the development of schizophrenia is the presence of genetic variations that affect the chemical structure of brain (Prasad et al., 2010). Schizophrenia symptoms depend on which neurotransmitter is present. the main transmitters that are related to schizophrenia 1)dopamine 2) serotonin 3) GABA 4) glutamine (Bansal & Chatterjee, 2021). People with schizophrenia have an increased sensitivity to dopamine compared to normal people, and this sensitivity is due to increased dopamine levels in presynaptic neurons or increased D2 receptors or high D2 receptors in the active stages of schizophrenia. (Seeman, 2013). However Regarding serotonin levels in people with schizophrenia, the following has been observed as a result of dysfunction associated with negative schizophrenia syndrome, and this imbalance is due to postsynaptic receptors being hypersensitive to 5HT. (Bleich et al., 1988). A previous study showed that The reduction in the levels of certain neurotransmitters, such as glutamatergic and gamma-aminobutyric acid (GABA), and the increased levels of these metabolites suggest that the disruption of the excitatory balance may be related to schizophrenia-spectrum disorders. (Nakahara et al., 2022).

2.4 Aim and Goals of the Thesis

The main aim of this project was to identify the possible gene and protein targets for establishing the relationship between early emerging sleep-related problems and the etiology of schizophrenia. To address this aim, the goals were designed as follows :

- Conducting a literature survey using text-mining methods to establish the research focuses among the studies on sleep disorders and schizophrenia

- Identifying the most frequently emerging sleep-related symptoms in schizophrenia patients using text-mining

- Identifying the most frequently emerging genes and proteins in studies on sleep disorders and schizophrenia

- Identifying the most frequently emerging genes and proteins for the most frequent sleep-related problems in schizophrenia

- Establishing functional relationships in obtained gene/protein list using gene enrichment over Gene Ontology databases

- After identifying the research trends for molecular etiology of sleep-related problems in schizophrenia, conducting a more detailed analysis of literature to identify the changes occurring in the target genes/proteins.

3. MATERIAL AND METHOD

The main *in silico* method utilized in this project was text-mining over the available scientific literature on PubMed and Google Scholar databases. For this purpose, CoreMine Medical, an online text-mining tool was utilized. The general workflow for the project is explained in Figure (1)

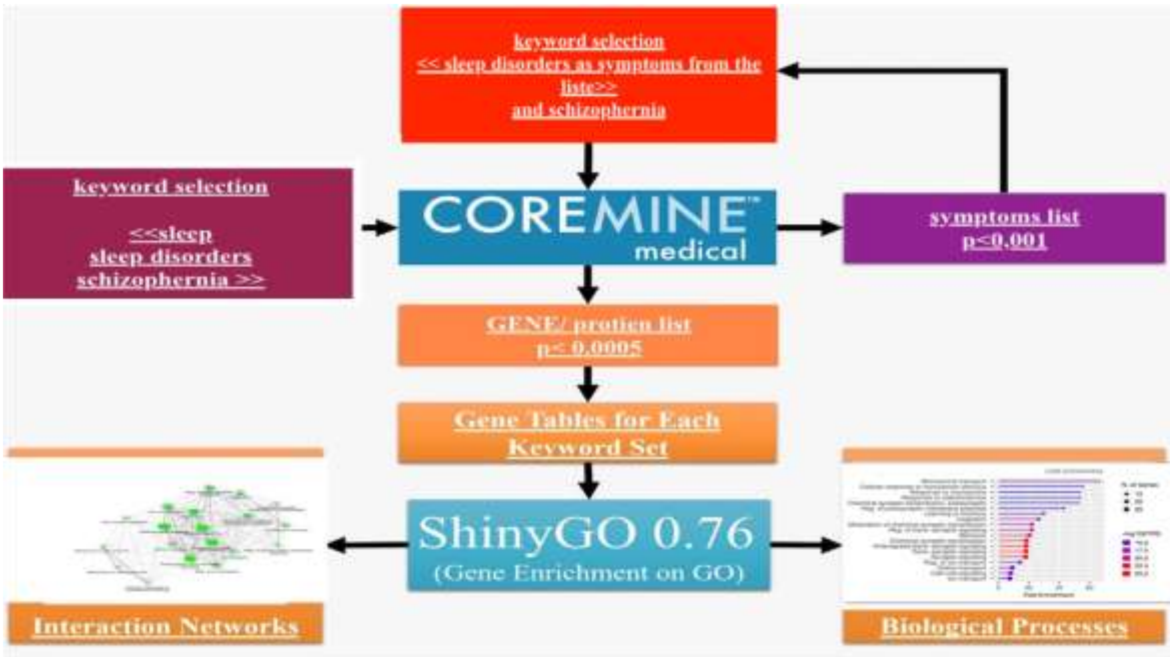

Figure 1: Text-miniging (core mine medical prosses) gene enrichment data by used ShinyGO

3.1. Core Mine Medical Platform

The COREMINE platform is the first of its kind to provide a domain-specific information community. The COREMINE Medical service is designed to provide medical professionals with the latest information about diseases and treatments. It also allows them to connect with other healthcare professionals and share their experiences. Through its unique features, biomedical researchers can easily navigate through multiple information networks and improve their knowledge of complex biological systems. This platform enables researchers from different fields of biosciences in research and drug design (Coremine Medical, n.d.).

The platform conducts a scientific literature survey on all available articles deposited in PubMed and Google Scholar. The algorithm takes in the keywords, grouped in subfields

such as diseases, biological processes etc., and reports findings in the intersection of the scanned literature with the given keywords in the following fields :

- Biomedical experts (Researchers working in the related field)
- Disease
- DRUG
- Symptom
- Procedure
- Anatomy
- Food
- Gene/ protein
- MeSH
- Chemical
- Cellular componene
- Biological process
- Molecular function
- Cell -lines
- Traditional Chinese medicine
- All categories

The reports in symptoms and gene/protein fields were used as the main data sources in this research.

Figure 2: The CoreMine Medical Interface. The report page for the platform is displayed.

3.2. Rules for Text-mining

3.2.1. Generalized Case for Sleep-related Problems in Schizophrenia

The text-mining over available scientific literature can provide valuable insight to accumulated information and can guide future hypotheses (Cohen and Hunter, 2008). In order to identify the genes that link sleep disorders and schizophrenia, following steps were performed on CoreMine Medical :

1. The genes that are at the intersection of research related to schizophrenia and sleep, selected keywords were "Schizophrenia (diseases) AND Sleep (biological process)". Resulting list of Genes/Proteins were downloaded and saved in .xls format. The level of significance for further analysis of this list was set at $p < 0.0005$.
2. To analyze the genes at the intersection of scientific papers on schizophrenia and sleep disorders, selected keywords were "Schizophrenia (disease) AND Sleep Disorders (disease)". Resulting list of Genes/Proteins and Symptoms were downloaded and saved in .xls format. The level of significance for further analysis of Gene/Protein list was set at $p < 0.0005$ and of Symptoms list at $p<0.001$.
3. The selected symptoms were then used as a keyword on their own, in the format "Schizophrenia (disease) AND __SYMPTOM__". Resulting list of Genes/Proteins were downloaded and saved in .xls format. The level of significance for further analysis of this list was set at $p < 0.0005$

The results that were converted into an Excel spreadsheet were further clustered under a single file with respect to the keywords.

3.3. Gene Enrichment and Gene Ontology

Gene enrichment is a useful analytical method to guide for analyzing data about gene expression that execute from a focus on gene sets, or clusters of genes with similar biological functions, chromosomal locations, or regulatory functions. Enrichment analysis can be used to determine if a group of genes detected in genome-wide research is enriched with genes belonging to a certain functional category or pathway, such as those revealed by gene ontology (GO) (Ashburner et al., 2000).

3.3.1 Gene Enrichment by ShinyGO

ShinyGO is an excellent tool for analyzing the various aspects of gene expression data, although its species coverage is not as broad as DAVID (The Database for Annotation, Visualization and Integrated Discovery) (Ge et al., 2020). DAVID provides a comprehensive set of tools that help investigators understand the biological significance of large gene lists. ShinyGO also utilized a set of tools are powered by the DAVID Database, which is a collection of functional annotations built on the Gene concept (Huang et al., 2007).ShinyGO also has a comprehensive set of gene sets related to humans, mice, and Arabidopsis targets (Ge et al., 2020). The unique features of the ShinyGO platform are its ability to display query genes on pathways diagrams and interactive networks, as well as its ability to visualize the overlaps between pathways. It also provides a statistical analysis of the differences in the gene type, length, and GC content between the background and the query genes. In order to enhance the capabilities of the platform, the ability to add other gene sets, such as the TF and miRNA target genes were also introduced (Ge et al., 2020). Fold enrichment t simply means how many fold more did something happen than you would expect by random chance, that is a fold enrichment of 2 means it happened twice as much as your random expectation.

(Dalmer & Clugston, 2019).A greater prior probability usually results in a lower FDR(False Discovery Rate). Consequently, the FDR has several helpful qualities when compared to the p-value. The FDR can be controlled in order to find as many important tests as feasible with a minimal amount of false positives. (Ji et al., 2011).ShinyGO was utilized in our research to gather the definitions of the gene symbols obtained by text-mining and to cluster them by the biological processes they are involved in. The results were displayed as networks and distribution graphs.

Figure 3: ShinyGo 0.76 Interface. The report page for the platform is displayed.

4. RESULTS

4.1. Sleep and Schizophrenia

The selected keywords were chosen to describe the various aspects of research related to sleep as “biological processes” and schizophrenia as “"diseases”. The resulting list was then saved in .xls format. The significance of these genes for further analysis was set at p<0.0005. The results are given in Table 1.

Table 1: Genes at the Intersection of “Sleep” and “Schizophrenia”. The 25 most significant genes are listed in the table.

Gene Symbol	Definition	Significance (p)
DISC1	DISC1 scaffold protein	0.00001959802416
CENPJ	centromere protein J	0.0000237282446
DTNBP1	dystrobrevin binding protein 1	0.0000273495484
HCRT	hypocretin neuropeptide precursor	0.00002896573489
DRD2	dopamine receptor D2	0.00005053180114
NRG1	neuregulin 1	0.00005783989995
ZNF804A	zinc finger protein 804A	0.00006004468051
HTR2A	5-hydroxytryptamine receptor 2A	0.00009362393991
COMT	catechol-O-methyltransferase	0.0001059547055
DRD3	dopamine receptor D3	0.0001071337707
PRL	prolactin	0.000167068614
SLC6A9	solute carrier family 6 member 9	0.0002223475032
RELN	reelin	0.0002377145911
NRXN1	neurexin 1	0.0002564809925
HTR2C	5-hydroxytryptamine receptor 2C	0.0002773319693
PDE10A	phosphodiesterase 10A	0.0002783219867
PVALB	parvalbumin	0.0002803313263
BDNF	brain derived neurotrophic factor	0.0002854076525
HTR1A	5-hydroxytryptamine receptor 1A	0.0002857915551
GRM3	glutamate metabotropic receptor 3	0.0003028171777

DRD4	dopamine receptor D4	0.0003194258005
SKAP2	src kinase associated phosphoprotein 2	0.0003664436602
BDNF-AS	BDNF antisense RNA	0.000370874875
PER3	period circadian regulator 3	0.0004277116635
HTR6	5-hydroxytryptamine receptor 6	0.0004814862591

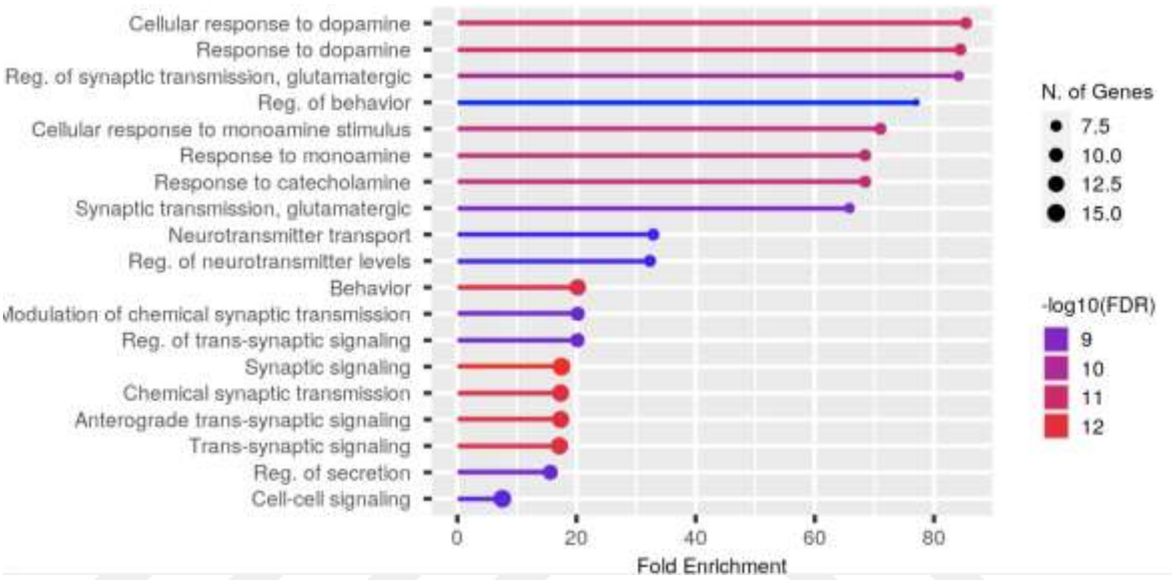

Figure 4: Gene Enrichment Results for Sleep and Schizophrenia.

Most of the genes in the list are grouped into sleep-related neurochemical systems, such as monoamines, glutamate, GABA and orexin. More detailed gene enrichment was performed for more specific search, as described in later sections.

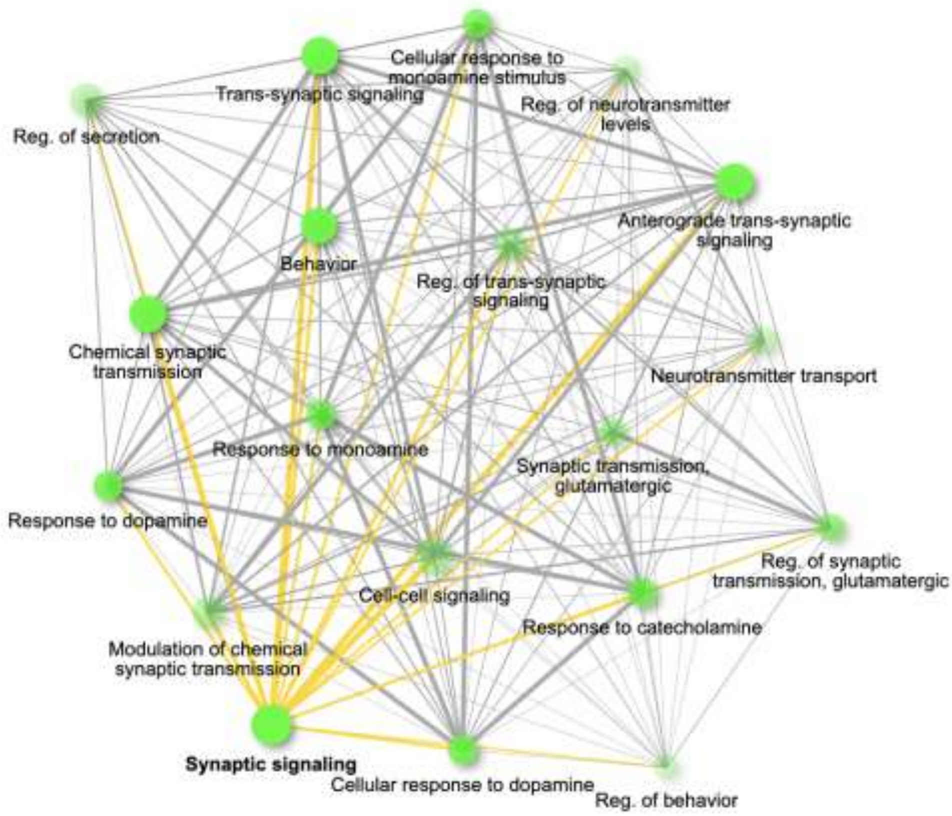

Figure 5: Gene Enrichment Network for "Sleep "and "Schizophrenia"

.the nodes identified in Figure 4 Are shown with relation .

4.2. Sleep Disorders and Schizophrenia

To analyze the genes at the intersection of scientific papers on schizophrenia and sleep disorders, selected keywords were "Schizophrenia (disease) AND Sleep Disorders (disease)". The resulting list of Genes/Proteins and Symptoms were downloaded and saved in .xls format. The level of significance for further analysis of Gene/Protein list was set at $p < 0.0005$ and of the Symptoms list at $p<0.001$. The results are given in Table 2**.**

Table 2: Genes at the Intersection of "Sleep disorders" and "Schizophrenia".

Gene Symbol	Definition	Significance
DISC1	DISC1 scaffold protein	0.00001267552232
DRD2	dopamine receptor D2	0.00003336273952
NRG1	neuregulin 1	0.00003708194053
COMT	catechol-O-methyltransferase	0.00006935021593
DRD3	dopamine receptor D3	0.00007149469064
HTR2A	5-hydroxytryptamine receptor 2A	0.0000745102839
HCRT	hypocretin neuropeptide precursor	0.0001194930276
RELN	reelin	0.0001479012755
CHRNA7	cholinergic receptor nicotinic alpha 7 subunit	0.00015032141
CHRFAM7A	CHRNA7 (exons 5-10) and FAM7A (exons A-E) fusion	0.0001554754274
NRXN1	neurexin 1	0.0001667556707
PRL	prolactin	0.0001689064497
PVALB	parvalbumin	0.0002000368936
BDNF	brain derived neurotrophic factor	0.0002082911385
DRD4	dopamine receptor D4	0.0002128818475
SKAP2	src kinase associated phosphoprotein 2	0.0002286087231
HTR2C	5-hydroxytryptamine receptor 2C	0.0002378670008
HTR1A	5-hydroxytryptamine receptor 1A	0.0002653670844
BDNF-AS	BDNF antisense RNA	0.0002715054032
HTR6	5-hydroxytryptamine receptor 6	0.0003371885974
CHRNA4	cholinergic receptor nicotinic alpha 4 subunit	0.0003526834613
GRIN1	neuregulin 1	0.0003943756553
CACNA1C	calcium voltage-gated channel subunit alpha1 C	0.0004598290405
DRD1	dopamine receptor D1	0.0004671504025
GRM5	glutamate metabotropic receptor 5	0.0004674573983

The 25 most significant genes are listed in the table.

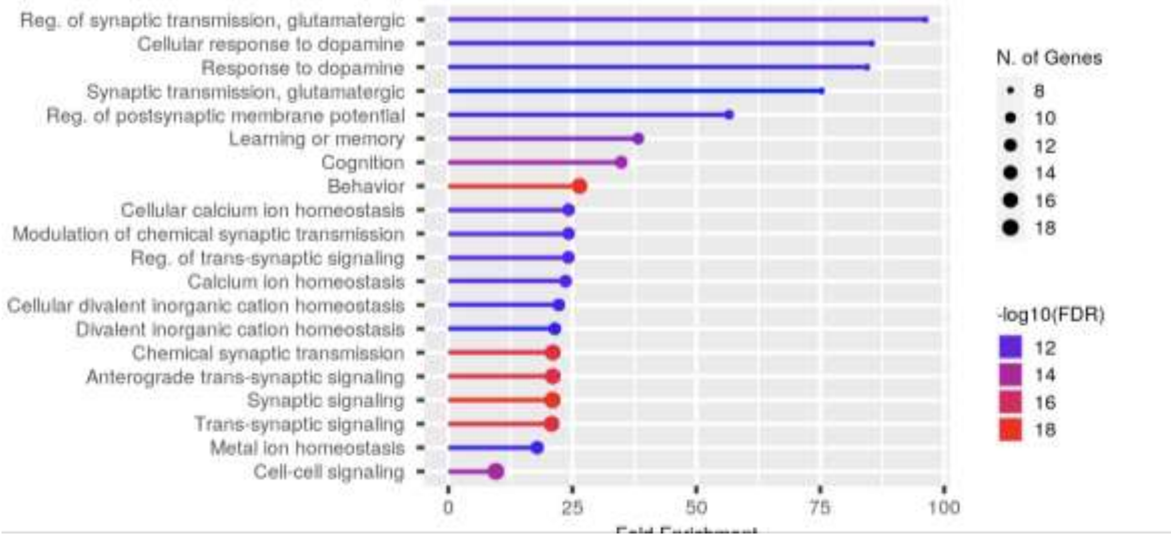

Figure 6: Gene Enrichment Results for" Sleep Disorders" and "Schizophrenia"

Most of the genes in the list are grouped into sleep-related neurochemical systems, in addition to synaptic processes and calcium homeostasis. Behaivoral nodes were mostly grouped under learning and memory. More detailed gene enrichment was performed for more specific search, as described in later sections.

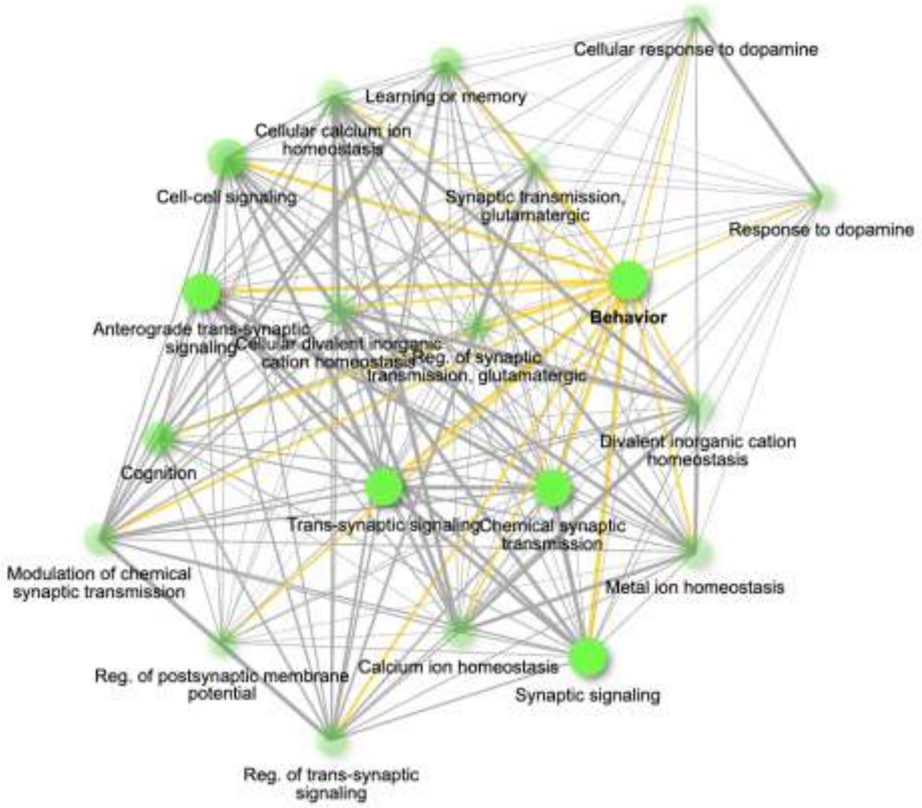

Figure 7: Gene Enrichment Network for "Sleep Disorders" and "Schizophrenia"

the nodes identified in Figure 6 are shown with relation.

4.3. Sleep-related Symptoms and Schizophrenia

The selected symptoms in the previous step were used as a keyword on their own, in the format "Schizophrenia (disease) AND __SYMPTOM__". The resulting list of Genes/Proteins was downloaded and saved in .xls format. The level of significance for further analysis of this list was set at $p < 0.001$. Almost 367 of different patterns of symptoms related to sleep disorders in schizophrenia were identified. Therefore, the symptoms were further classified as directly related to sleep or not. The results are given in Table 3. For further analysis, only the directly sleep-related symptoms were used as keywords.

Table 3: Symptoms Related to Sleep and Associated with Schizophrenia.

Symptom	Classification	Significance (p)
Sleep disturbances	Sleep-related	0.0000003201072047
Psychotic symptoms	Other	0.000002678479407
Positive and negative symptoms	Other	0.000002927325848
Sleep difficult	Sleep-related	0.0000048739106
Sleeplessness	Other	0.000007775348656
Auditory hallucinations	Other	0.000009193840609
Excessive daytime somnolence	Sleep	0.00001067918394
Hypersomnia	Sleep	0.00001341980799
Catatonia	Other	0.00001654760769
Psychiatric symptom	Other	0.00002195523377
Neurobehavioral manifestations	Other	0.00002244571343
Neurological soft signs	Other	0.000028278438
Affective symptoms	Other	0.00003415608535
Impaired sleep	Sleep	0.00004203358426
Snoring	Sleep	0.00004816588153
Depressive symptoms	Other	0.00005336270878
Prodrome	Other	0.0000746434949
Involuntary movements	Other	0.00007506655289
Fatigue	Other	0.00008860133459
Early awakening	Sleep	0.00009537689136
Agitation	Other	0.0001071464049
Respiratory dysfunction	Other	0.0001180610754
Hypersomnolence	Sleep	0.0001227940477

Hypnagogic hallucinations	Other	0.0001487417618
Social stigmata	Other	0.000162521449
Visual hallucinations	Other	0.0002085971131
Behavioral symptoms	Other	0.0002103957612
Nocturnal myoclonus	Sleep	0.0002393412049
Mannerism	Other	0.000260797611
Indifferent mood	Other	0.0003175729007
Enuresis	Other	0.000363563271
Verbal auditory hallucinations	Other	0.0003766051731
Polydipsia	Other	0.0003766851952
Dystonia	Other	0.000464733729
Bedwetting	Other	0.0005049705273
Seizures	Other	0.0006608667931
Psychological symptom	Other	0.000840128403
Sedation	Other	0.0008785204551
Secondary insomnia	Sleep	0.0008860758252
Hot flushes	Other	0.0008946634067
Hypokinesia	Other	0.0009215032191
Headache	Other	0.0009673614735
Tremor	Other	0.001232588116
Myoclonus	Other	0.001233782187
Motor restlessness	Other	0.001365246157
Multiples symptoms	Other	0.0014096198
Chronic pain	Other	0.001411557617
Personality change	Other	0.001517792428
Dizziness	Other	0.001581572122
Absence of sensation	Other	0.001604737502
Fatigue symptom	Other	0.001719603563
Menopausal symptoms	Other	0.001802879761
Excessive urination at night	Other	0.00181265645
Withdrawal symptoms	Other	0.001876579425
Rebound insomnia	Sleep	0.001993709891
Vertigo	Other	0.002362827565
Excitability	Other	0.002503058701
Mood elevated	Other	0.002585836815

Diarrhea	Other	0.002649832982
Posturing	Other	0.002810816119
Physical symptom	Other	0.002853716317
Constipation	Other	0.00309418937
Motor dysfunction	Other	0.003225093793
Bradykinesia	Other	0.003356946464
Sensory hallucinations	Other	0.004006150982
Muscle rigidity	Other	0.004059576455
Electroencephalography phase synchronization	Other	0.004351116444
Alexithymia	Other	0.004646049984
Angina pectoris	Other	0.005007070037
Motor symptom	Other	0.005143460369
Flexed fetal attitude	Other	0.005222915231
Associated symptom	Other	0.005457374342
Stiffness	Other	0.005468995864
Motor manifestations	Other	0.005497793468
Regurgitation	Other	0.006313833051
Respiratory distress	Other	0.006450513199
Stress symptoms	Other	0.006710931678
Abdominal pain	Other	0.006812921439
Cerebellar ataxia	Other	0.006905699767
Absence of pain sensation	Other	0.006946185914
Night sweat	Other	0.0070202393
Fugue state	Other	0.007100589626
Nervousness	Other	0.007123060185
Orofacial pain	Other	0.00732127243
Acute stress	Other	0.007396012353
Ataxia	Other	0.007472279064
Jaundice (not of newborn)	Other	0.007606086618
Respiratory abnormalities	Other	0.007615600102
Polyuria	Other	0.007620708735
Erythema	Other	0.00763303484
Memory loss	Other	0.007725307548
Muscle cramp	Other	0.007725904086
Focal seizures	Other	0.008568519635

Spots on skin	Other	0.009645329852
Mental exhaustion	Other	0.01002192848
Nasal congestion	Other	0.01011148301
Chest pain	Other	0.01021710227
Overweight	Other	0.01060761747
Hangover from any alcohol or other drugs substance	Other	0.01065426536
Hangover from alcohol	Other	0.01065426536
Feeling despair	Other	0.01098290801
Motor tic	Other	0.01122892806
Flushing	Other	0.01142597033
Organ failure	Other	0.01158305617
Starvation	Other	0.01199446359
Signs and symptoms	Other	0.01280978043
Hunger	Other	0.01484121086
Pain	Other	0.01502466462
Tonic clonic seizures	Other	0.01523419399
Postoperative pain	Other	0.01524720451
Generalized aches and pains	Other	0.01577205099
Erection pain	Other	0.01622120563
Hemoptysis	Other	0.01626084202
Increased sweating	Other	0.01686127844
Nausea	Other	0.01710338417
Cogwheel rigidity	Other	0.0173573886
Fluctuation	Other	0.01788421825
Low back pain	Other	0.01803929264
Forgetfulness	Other	0.01872705329
Facial pain	Other	0.01889771642
Hyperexplexia	Other	0.01922705124
Flatulence	Other	0.02007154835
Coughing	Other	0.02009826819
Muscle twitch	Other	0.0201521262
Heartburn	Other	0.02057565859
Macule	Other	0.02108527098
Asthenia	Other	0.02144379486
Drug withdrawal symptoms	Other	0.02190219827

Feeling tire	Other	0.02190219827
Impaired motor coordination	Other	0.02245802233
Vague ill health	Other	0.02420856794
Hepatomegaly	Other	0.02425851799
Natural hypothermia	Other	0.02468739915
Ache	Other	0.02575061641
Recovery of function	Other	0.02627288277
Subjective tinnitus	Other	0.02628282717
Leg discomfort	Other	0.02646437285
Sensory discomfort	Other	0.02661674045
Abnormal coordination	Other	0.02667676023
Panic symptoms	Other	0.02868403676
Chills	Other	0.02877648752
Carbohydrate cravings	Other	0.02950170113
Vocal tic	Other	0.02961090619
Pregnancy mood swing	Other	0.03001454964
Hyperoxia	Other	0.03035168158
Malaise	Other	0.03068213507
Body pain	Other	0.03112997288
Heartburn acidity	Other	0.03135296104
Paresis	Other	0.03232285387
Cachexia	Other	0.03304782808
Decrease in appetite	Other	0.03314063195
Drooling	Other	0.03337893817
Multiple somatic complaints	Other	0.03411581335
Sciatica	Other	0.0345762399
Pruritus	Other	0.03523193146
Pelvic pain	Other	0.03534113652
Body weight problem	Other	0.03560692703
Sore to touch	Other	0.03561203401
Pricks skin	Other	0.035902684
Laryngeal dystonia	Other	0.03775260256
Situational stress general	Other	0.03837850846
Burning sensation	Other	0.04321383026
Emotional shock	Other	0.04386790514

Decreased libido	Other	0.04409206914
Hemiplegia	Other	0.0442521794
Resting tremor	Other	0.04672216271
Change in mental status	Other	0.04672640639
Stridor	Other	0.04831918256
Postoperative nausea and vomiting	Other	0.04962044127
Lethargy	Other	0.05103872885
Consciousness disturbance	Other	0.05155583614
Fatigability	Other	0.05283743853
Sluggishness	Other	0.05353969083
Hoarseness	Other	0.05449854493
Flank pain	Other	0.05576948196
Abnormal sensation	Other	0.05656162234
Dyspnea	Other	0.05664768018
Feeling jittery	Other	0.05732251942
Virilism	Other	0.05777400752
Central pain	Other	0.0578167858
Ophthalmoplegia	Other	0.05793803565
Frequent headaches	Other	0.05846863076
Cyanosis	Other	0.0586275123
Hematemesis	Other	0.05954162825
Fever of unknown origin	Other	0.0618391586
Neuralgia	Other	0.06263117465
Very low birth weight	Other	0.06368778491
Fine tremor	Other	0.06374944982
Clumsiness	Other	0.06461646241
Physical suffering	Other	0.06859505562
Pelvic pain female	Other	0.0698782172
Distress gastrointestinal	Other	0.07024872145
Blepharospasm	Other	0.07341302635
Spasm	Other	0.07521319423
Dryness of eye	Other	0.07549084404
Sexual symptoms	Other	0.0761037979
Pregnancy related skin change	Other	0.07803728555
Weakness	Other	0.07810481696

Mechanical allodynia	Other	0.07952259172
Sore throat	Other	0.07966919116
Convulsions	Other	0.08014364406
Cardiovascular problem	Other	0.08021335986
Dysuria	Other	0.08033920093
Visceral pain	Other	0.08831571031
Local reaction	Other	0.0898760523
Hypoproteinemia	Other	0.09052399803
Lightheadedness	Other	0.09523065907
Pallor	Other	0.09542108907
Exercise intolerance	Other	0.09756729887
Paraparesis	Other	0.1013066934
Hip pain	Other	0.1017638064
Hypalgesia	Other	0.1024986822
Laziness	Other	0.1028928578
Acute onset pain	Other	0.1050827662
Flaccid paralysis	Other	0.1063439917
Swollen joint	Other	0.1113891248
Digestive problem	Other	0.11230516
Hyperalgesia	Other	0.1150226414
Respiratory signs and symptoms	Other	0.1154697481
Abdominal pain lower	Other	0.1174036576
Muscle spasticity	Other	0.1187988923
Jaw pain	Other	0.121283638
Tissue pain	Other	0.1223504353
Skin manifestations	Other	0.123954116
Heart problem	Other	0.125738689
Chronic cough	Other	0.1277500789
Allergic symptom	Other	0.1283953422
Labor pain	Other	0.12857014
Abdominal pain upper	Other	0.129194127
Back pain	Other	0.132597694
Premenstrual symptoms	Other	0.1348482895
Dry cough	Other	0.1379306054
Polymyalgia	Other	0.1384364655

Hepatosplenomegaly	Other	0.1450645005
Muscle hypotonia	Other	0.1455971743
Exhaustion	Other	0.1477441869
Nociceptive pain	Other	0.1479532262
Male sexual dysfunction	Other	0.149501332
Symptoms gastrointestinal	Other	0.1515387102
Sense of smell altered	Other	0.1519548022
Nausea chronic	Other	0.1519548022
Gasping for breath	Other	0.1553775478
Drop foot gait	Other	0.156049179
Muscular fasciculation	Other	0.1584392414
Breath holding	Other	0.1616378866
Respiratory problems	Other	0.1660253616
Chest pressure	Other	0.1688170967
Asterixis	Other	0.175282364
Orthostasis	Other	0.1759332765
Eye pain	Other	0.1768237038
Epigastric abdominal pain	Other	0.1780867266
Parkinsonian tremor	Other	0.1785866404
Convulsive seizures	Other	0.1823206828
Secondary enuresis	Other	0.18753467
Cervical dystonia	Other	0.1886450824
Dyspepsia	Other	0.1904533062
Pain in lower limb	Other	0.1904772565
Rhinorrhea	Other	0.1924419692
Static tremor	Other	0.1947657662
Drop attack	Other	0.1949575474
High weight	Other	0.1976298865
Cardiovascular symptoms	Other	0.2002938378
Neurologic signs	Other	0.201474732
Postoperative nausea	Other	0.2019059711
Taste sweet	Other	0.2056144419
Dyspnea on exertion	Other	0.2103441914
Syncope	Other	0.2121388476
Lassitude	Other	0.2152923023

Pain inflammatory	Other	0.2200548156
Facial paresis	Other	0.2213549798
Photopsia	Other	0.2230322899
Cutaneous symptom	Other	0.2297841167
Pyramidal signs	Other	0.2400531649
Athetosis	Other	0.2404965977
Sleep disturbances	Other	0.00000320107204738917
Psychotic symptoms	Other	0.1591948737
Positive and negative symptoms	Other	0.1599379729
Sleep difficult	Other	0.160681072
Sleeplessness	Other	0.1614241712
Extrapyramidal signs	Other	0.1621672703
Auditory hallucinations	Other	0.1629103695
Excessive daytime somnolence	Other	0.1636534686
Hypersomnia	Other	0.1643965678
Catatonia	Other	0.1651396669
Psychiatric symptom	Other	0.1658827661
Neurobehavioral manifestations	Other	0.1666258652
Neurological soft signs	Other	0.1673689644
Affective symptoms	Other	0.1681120636
Impaired sleep	Other	0.1688551627
Snoring	Other	0.1695982619
Depressive symptoms	Other	0.170341361
Prodrome	Other	0.1710844602
Involuntary movements	Other	0.1718275593
Fatigue	Other	0.1725706585
Early awakening	Other	0.1733137576
Agitation	Other	0.1740568568
Respiratory dysfunction	Other	0.1747999559
Hypersomnolence	Other	0.1755430551
Hypnagogic hallucinations	Other	0.1762861542
Social stigmata	Other	0.1770292534
Visual hallucinations	Other	0.1777723525
Behavioral symptoms	Other	0.1785154517
Nocturnal myoclonus	Other	0.1792585508

Mannerism	Other	0.18000165
Indifferent mood	Other	0.1807447491
Enuresis	Other	0.1814878483
Verbal auditory hallucinations	Other	0.1822309474
Polydipsia	Other	0.1829740466
Dystonia	Other	0.1837171457
Bedwetting	Other	0.1844602449
Seizures	Other	0.185203344
Psychological symptom	Other	0.1859464432
Sedation	Other	0.1866895423
Secondary insomnia	Other	0.1874326415
Hot flushes	Other	0.1881757406
Hypokinesia	Other	0.1889188398
Headache	Other	0.1896619389
Tremor	Other	0.1904050381
Myoclonus	Other	0.1911481372
Motor restlessness	Other	0.1918912364
Multiples symptoms	Other	0.1926343355
Chronic pain	Other	0.1933774347
Personality change	Other	0.1941205339
Dizziness	Other	0.194863633
Absence of sensation	Other	0.1956067322
Fatigue symptom	Other	0.1963498313
Menopausal symptoms	Other	0.1970929305
Excessive urination at night	Other	0.1978360296
Withdrawal symptoms	Other	0.1985791288
Rebound insomnia	Other	0.1993222279
Vertigo	Other	0.2000653271
Excitability	Other	0.2008084262
Mood elevated	Other	0.2015515254
Diarrhea	Other	0.2022946245
Posturing	Other	0.2030377237
Physical symptom	Other	0.2037808228
Constipation	Other	0.204523922
Motor dysfunction	Other	0.2052670211

Bradykinesia	Other	0.2060101203
Sensory hallucinations	Other	0.2067532194
Muscle rigidity	Other	0.2074963186
Electroencephalography phase synchronization	Other	0.2082394177
Alexithymia	Other	0.2089825169
Angina pectoris	Other	0.209725616
Motor symptom	Other	0.2104687152
Flexed fetal attitude	Other	0.2112118143
Associated symptom	Other	0.2119549135
Stiffness	Other	0.2126980126
Motor manifestations	Other	0.2134411118
Regurgitation	Other	0.2141842109
Respiratory distress	Other	0.2149273101
Stress symptoms	Other	0.2156704092
Abdominal pain	Other	0.2164135084
Cerebellar ataxia	Other	0.2171566075
Absence of pain sensation	Other	0.2178997067
Night sweat	Other	0.2186428058
Fugue state	Other	0.219385905
Nervousness	Other	0.2201290041
Orofacial pain	Other	0.2208721033
Acute stress	Other	0.2216152025
Ataxia	Other	0.2223583016
Jaundice (not of newborn)	Other	0.2231014008
Respiratory abnormalities	Other	0.2238444999
Polyuria	Other	0.2245875991
Erythema	Other	0.2253306982
Memory loss	Other	0.2260737974
Muscle cramp	Other	0.2268168965
Focal seizures	Other	0.2275599957
Spots on skin	Other	0.2283030948
Mental exhaustion	Other	0.229046194
Nasal congestion	Other	0.2297892931
Chest pain	Other	0.2305323923
Overweight	Other	0.2312754914

Hangover from any alcohol or other drugs substance	Other	0.2320185906
Hangover from alcohol	Other	0.2327616897
Feeling despair	Other	0.2335047889
Motor tic	Other	0.234247888
Flushing	Other	0.2349909872
Organ failure	Other	0.2357340863
Starvation	Other	0.2364771855
Signs and symptoms	Other	0.2372202846
Hunger	Other	0.2379633838
Pain	Other	0.2387064829
Tonic clonic seizures	Other	0.2394495821
Postoperative pain	Other	0.2401926812
Generalized aches and pains	Other	0.2409357804
Erection pain	Other	0.2416788795
Hemoptysis	Other	0.2424219787
Increased sweating	Other	0.2431650778
Nausea	Other	0.243908177
Cogwheel rigidity	Other	0.2446512761
Fluctuation	Other	0.2453943753
Low back pain	Other	0.2461374744
Forgetfulness	Other	0.2468805736
Facial pain	Other	0.2476236727
Hyperexplexia	Other	0.2483667719
Flatulence	Other	0.2491098711
Coughing	Other	0.2498529702
Muscle twitch	Other	0.2505960694
Heartburn	Other	0.2513391685
Macule	Other	0.2520822677
Asthenia	Other	0.2528253668
Drug withdrawal symptoms	Other	0.253568466
Feeling tire	Other	0.2543115651

All the symptoms obtained from text-mining is listed with p values.

4.4 .Symptom-related Classification

4.4.1. Sleep Disturbance and Schizophrenia

The selected keywords were chosen to describe the various aspects of research related to sleep disturbance and schizophrenia. The resulting list was then saved in .xls format. The significance of these genes for further analysis was set at $p<0.001$ The results are given in Table 4.

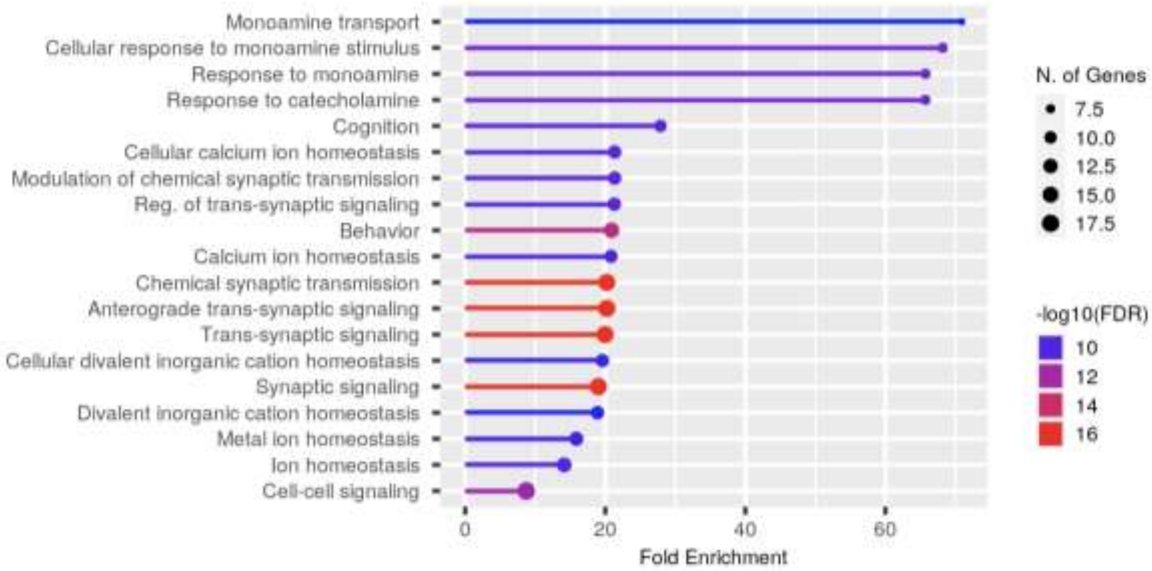

Figure 8: Gene Enrichment Results for Sleep Disturbance and Schizophrenia.

Most of the genes in the list are grouped into transsynaptic processes. The strongest enrichment was observed for monoamine-related processes.

The nodes identified in Figure 8 are shown with relation.

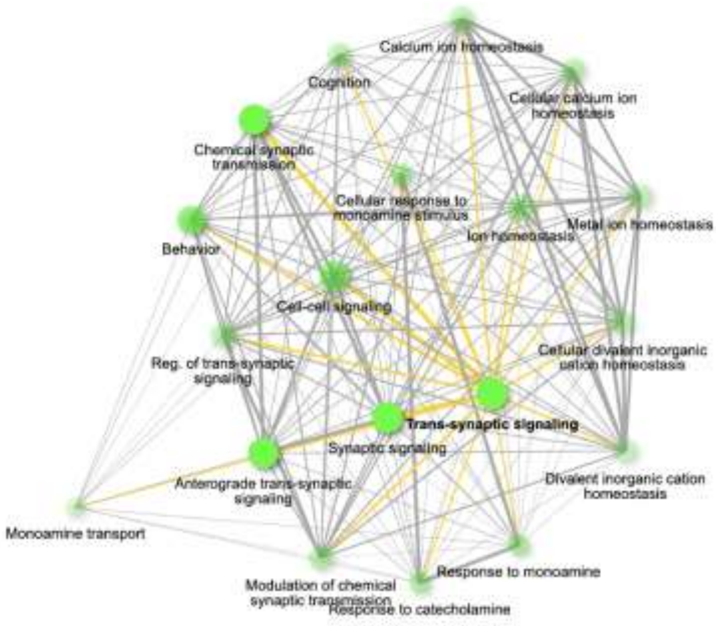

Figure 9: Gene Enrichment Network for “Sleep Disturbance “and “Schizophrenia”.

Table 4: Genes at the Intersection of "Sleep disturbance" and "Schizophrenia"

Gene Symbol	Definition	Significance (p)
DISC1	DISC1 scaffold protein	0.00001175926317
DRD2	dopamine receptor D2	0.00003077652498
COMT	catechol-O-methyltransferase	0.00006514243425
HTR2A	5-hydroxytryptamine receptor 2A	0.00006934426181
HCRT	hypocretin neuropeptide precursor	0.0001334162903
CHRNA7	cholinergic receptor nicotinic alpha 7 subunit	0.0001392718674
CHRFAM7A	CHRNA7 (exons 5-10) and FAM7A (exons A-E) fusion	0.0001440386736
PRL	prolactin	0.0001549919863
PVALB	parvalbumin	0.0001838447413
BDNF	brain derived neurotrophic factor	0.000191691245
SKAP2	src kinase associated phosphoprotein 2	0.0002108201546
HTR2C	5-hydroxytryptamine receptor 2C	0.0002209792862
HTR1A	5-hydroxytryptamine receptor 1A	0.0002474215969
BDNF-AS	BDNF antisense RNA	0.0002528120198
HTR6	5-hydroxytryptamine receptor 6	0.0003174027616
CHRNA4	cholinergic receptor nicotinic alpha 4 subunit	0.0003493417009
GRIN1	glutamate ionotropic receptor NMDA type subunit 1	0.0003673944874
GRM2	glutamate metabotropic receptor 2	0.0003930910912
CACNA1C	calcium voltage-gated channel subunit alpha1 C	0.0004230545753
GRM5	glutamate metabotropic receptor 5	0.0004286894355
DRD1	dopamine receptor D1	0.0004294015106
IGLON5	IgLON family member 5	0.000513167083
SLC6A3	solute carrier family 6 member 3	0.0005459426382
APP	amyloid beta precursor protein	0.0005868108566
NDOR1	NADPH dependent diflavin oxidoreductase	0.0006151497818
HTR7	5-hydroxytryptamine receptor 7	0.0006251093698

. The 25 most significant genes are listed in the table.

4.4.2. Insomnia and Schizophrenia

The symptoms that can be grouped under insomnia were “early awakening”, “sleeplessness”, “sleep difficulty”, “secondary insomnia”. Each symptom was used as an independent keyword together with schizophrenia. The resulting lists were then saved in .xls format. The significance of these genes for further analysis was set at $p<0.001$. The results are given in Table 5,6,7. Gene enrichment was not performed for the genes at the intersection of “early awakening” and “schizophrenia” as there were only three genes, two of which were BDNF-related. No significant gene target was found in relation to secondary insomnia and schizophrenia.

Table 5: Genes at the Intersection of “ Early awakening ” and “Schizophrenia”

Gene Symbol	Definition	Significance(p)
PRL	prolactin	0.0001363099195
BDNF	brain derived neurotrophic factor	0.0001722249134
BDNF-AS	BDNF antisense RNA	0.0002277794046

The genes with p<0.001 are listed, Only prolactin and BDNF emerged as direct targets.

Table 6: Genes at the Intersection of "sleeplessness" and "Schizophrenia"

Gene Symbol	Definition	Significance (p)
DRD2	dopamine receptor D2	0.00003106282197
COMT	catechol-O-methyltransferase	0.00006478171231
DRD3	dopamine receptor D3	0.00006591377081
HTR2A	5-hydroxytryptamine receptor 2A	0.00006630788315
NRXN1	neurexin 1	0.0001558471576
PRL	prolactin	0.0001582235035
PVALB	parvalbumin	0.0001856772841
BDNF	brain derived neurotrophic factor	0.0001860024572
HCRT	hypocretin neuropeptide precursor	0.0001935289182
DRD4	dopamine receptor D4	0.000198248849
HTR1A	5-hydroxytryptamine receptor 1A	0.0002179036012
SKAP2	src kinase associated phosphoprotein 2	0.0002189291088
HTR2C	5-hydroxytryptamine receptor 2A	0.0002250229474
BDNF-AS	BDNF antisense RNA	0.0002442142393
ERBB4	Erb-B2 Receptor Tyrosine Kinase 4	0.0002931703815
HTR6	5-hydroxytryptamine receptor 6	0.0003144371357
PRODH	Proline Dehydrogenase 1	0.000323655723
CHRNA4	cholinergic receptor nicotinic alpha 4 subunit	0.0003530485361
GRIN1	glutamate ionotropic receptor NMDA type subunit 1	0.0003681030808
PRNP	Prion Protein	0.0003803142021
GRM2	glutamate metabotropic receptor 2	0.0003970119473
CACNA1C	calcium voltage-gated channel subunit alpha1 C	0.0004212786066
DRD1	dopamine receptor D1	0.0004226047091
GRM5	glutamate metabotropic receptor 5	0.0004285111373
GABRB2	Gamma-Aminobutyric Acid Type A Receptor Subunit Beta2,	0.0004578290767
GAD1	Glutamate decarboxylase 1	0.0005332003707
SLC6A3	solute carrier family 6 member 3	0.0005728972308
NDOR1	Nuclear Receptor Corepressor 1	0.0006215489481

HTR7	5-hydroxytryptamine receptor 7	0.0006594265395
CYP2D6	cytochrome P450 family 2 subfamily D member 6	0.0006843743998
SLC6A4	solute carrier family 6 member 4	0.0007014829212
APP	amyloid beta precursor protein	0.0007068064645
GRIN2B	glutamate ionotropic receptor NMDA type subunit 2B	0.0007254518849
ANK3	Ankyrin 3	0.0007400103946
TAAR1	trace amine associated receptor 1	0.0008606664024
GRIN2A	glutamate ionotropic receptor NMDA type subunit 2A	0.0009445690928

The genes with p<0.001 are listed.

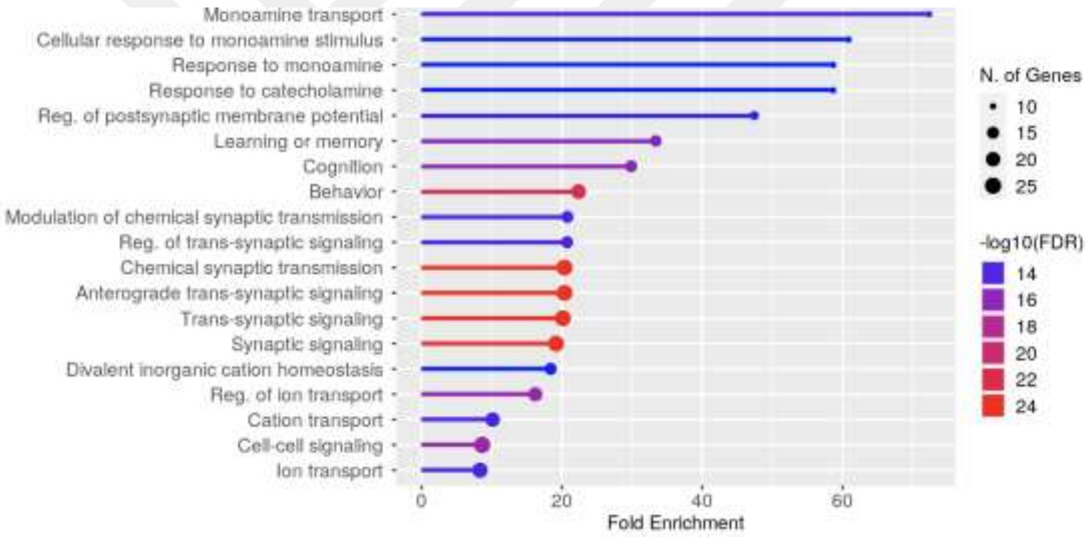

Figure 10: Gene Enrichment Results for "Sleeplessness "and "Schizophrenia."

Most of the genes in the list are grouped into transsynaptic processes. The strongest enrichment was observed for dopamine-related

processes.

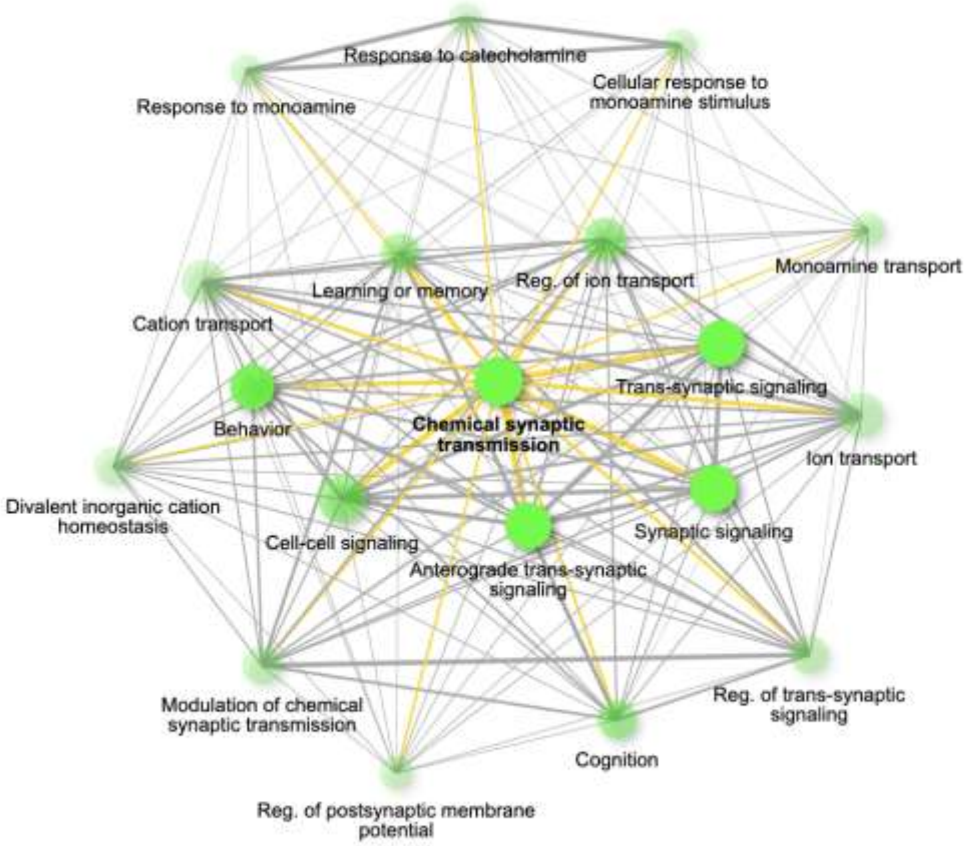

Figure 11: Gene Enrichment Network for " Sleeplessness "and "Schizophrenia"

The nodes identified in Figure 10 Are shown with relation .

Table 7: Genes at the Intersection of " Sleep Difficulty" and "Schizophrenia"

Gene Symbol	Definition	Significance(p)
DRD2	dopamine receptor D2	0.0000282638089
COMT	catechol-O-methyltransferase	0.00005959119891
HTR2A	5-hydroxytryptamine receptor 2A	0.00006460440603
PRL	prolactin	0.0001432831695
BDNF	brain derived neurotrophic factor	0.0001757684416
SKAP2	src kinase associated phosphoprotein 2	0.000197156472
BDNF-AS	BDNF antisense RNA	0.0002319959002
CACNA1C	calcium voltage-gated channel subunit alpha1 C	0.0003964459611
CYP2D6	cytochrome P450 family 2 subfamily D member 6	0.0006643065958
SLC6A4	solute carrier family 6 member 4	0.0007051475994
APP	amyloid beta precursor protein	0.0007327069177

The genes with $p<0.001$ are listed.

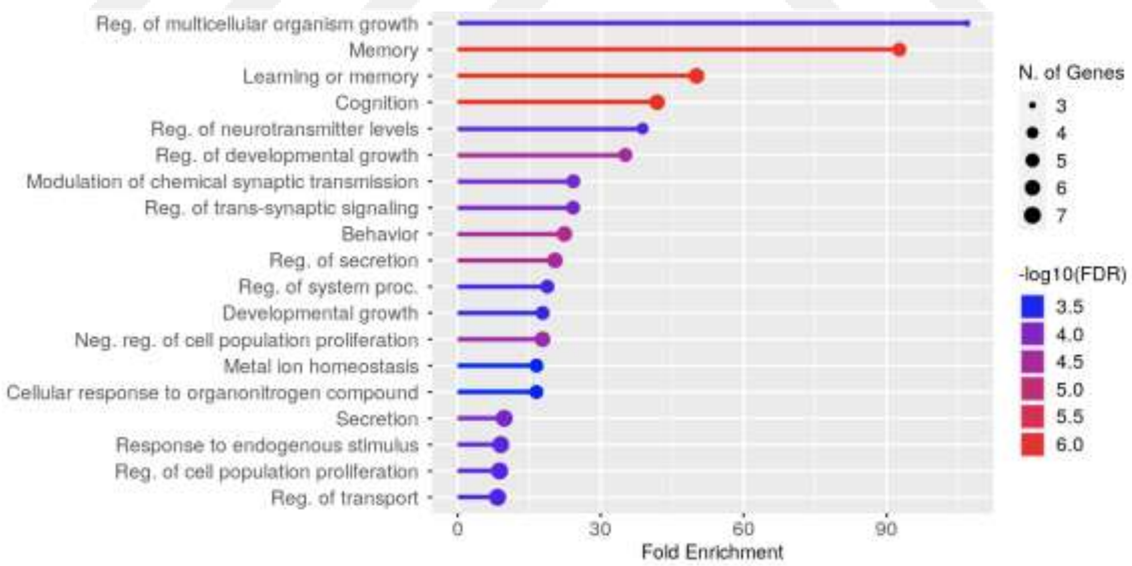

Figure 12: Gene Enrichment Results for "Sleep Difficulty "and "Schizophrenia"

Most of the genes in the list are grouped into cognitive processes, i.e. learning and memory. The strongest enrichment was observed for growth-related processes.

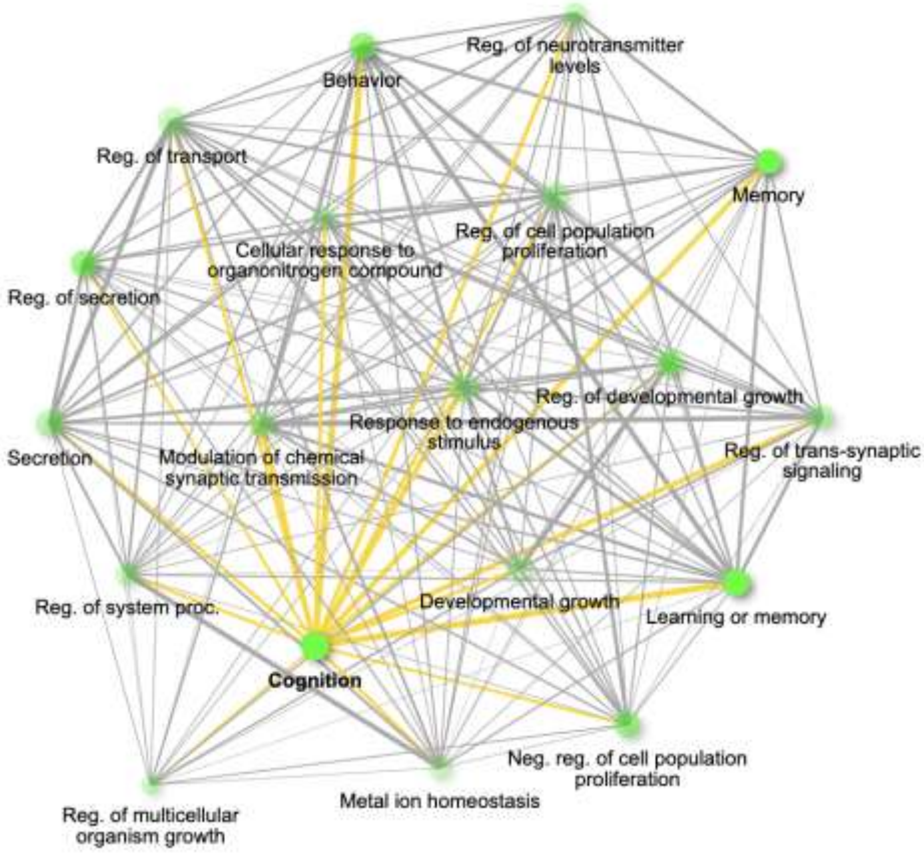

Figure 13: Gene Enrichment Network for " Sleep Difficulty "and "Schizophrenia"

the nodes identified in Figure 12 Are shown in relation.

4.4.3 Hypersomnia and Schizophrenia

The symptoms that can be grouped under hypersomnia were "Excessive daytime somnolence", "hypersomnia", "hypersomnolence". Each symptom was used as an independent keyword together with schizophrenia.. The resulting list was then saved in .xls format. The significance of these genes for further analysis was set at $p<0.001$. The results are given in Table 3. The results are given in Table 8,9,10.

Table 8: Genes at the Intersection of "Excessive daytime somnolence" and "Schizophrenia".

The most significant genes are listed in the table .

Gene Symbol	Definition	Significance (p)
APP	amyloid beta precursor protein	0.0007199026814
BDNF	brain derived neurotrophic factor	0.0001762565087
BDNF-AS	BDNF antisense RNA	0.0002326360095
CACNA1C	calcium voltage-gated channel subunit alpha1 C	0.000377042103
CHRNA4	cholinergic receptor nicotinic alpha 4 subunit	0.0003082874724
COMT	catechol-O-methyltransferase	0.00005816251608
CYP2D6	cytochrome P450 family 2 subfamily D member 6	0.0006535422316
DRD1	dopamine receptor D1	0.0003768968548
DRD2	dopamine receptor D2	0.0000276256207
DRD3	dopamine receptor D3	0.00005869119016
GRM5	glutamate metabotropic receptor 5	0.0003750499102
HCRT	hypocretin neuropeptide precursor	0.0003242021192
HTR1A	5-hydroxytryptamine receptor 1A	0.0002252465528
HTR2A	5-hydroxytryptamine receptor 2A	0.0000628511473
HTR2C	5-hydroxytryptamine receptor 2C	0.0002083189126
PRL	prolactin	0.0001410706204
SLC6A3	solute carrier family 6 member 3	0.0005406318702
SLC6A4	solute carrier family 6 member 4	0.0006874612048
TAAR1	trace amine associated receptor 1	0.0007197406431

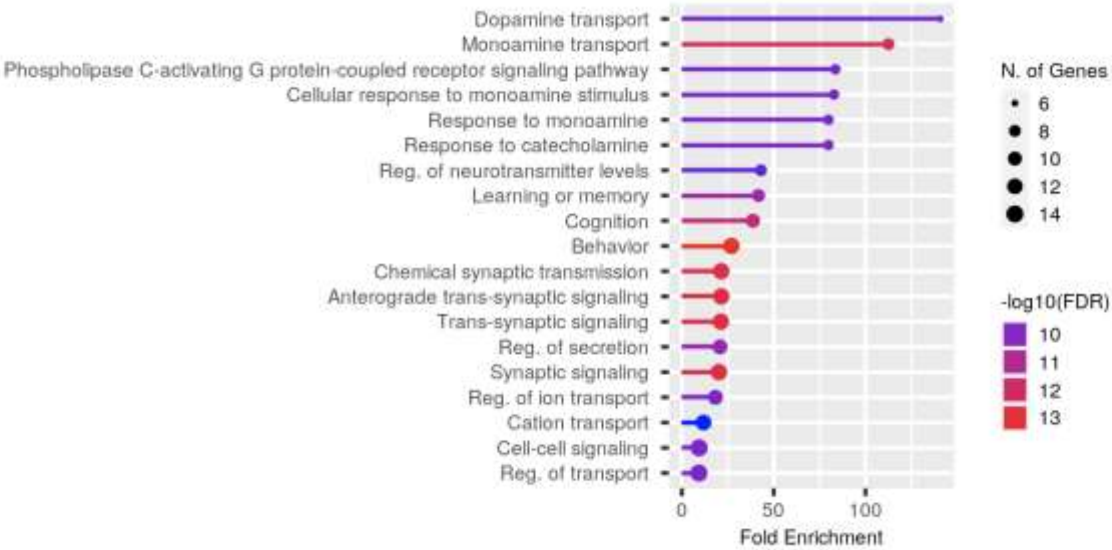

Figure 14: Gene Enrichment Results for "Excessive daytime somnolence "and "Schizophrenia".

Most of the genes in the list are grouped into behavior,. The strongest enrichment was observed for Dopamine transport processes.

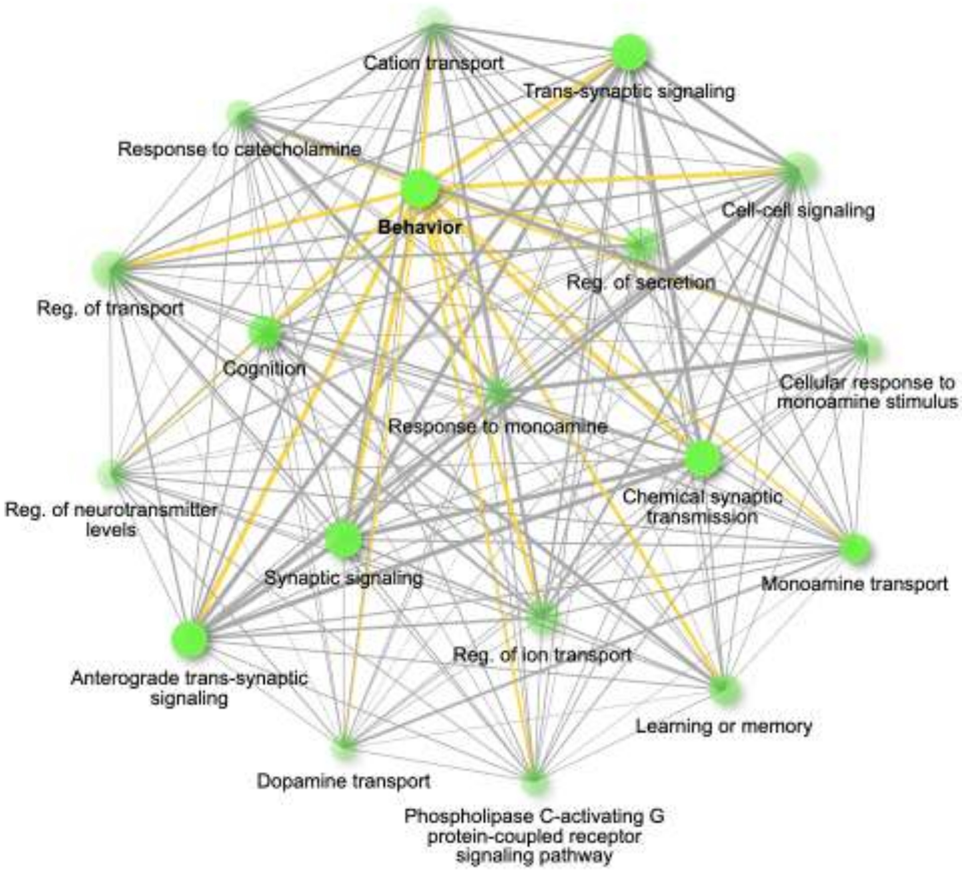

Figure 15: Gene Enrichment Network for "Excessive daytime somnolence " and "Schizophrenia"

.the nodes identified in Figure 14 Are shown with relation.

Table 9: Genes at the Intersection of " hypersomnia" and "Schizophrenia".

The most significant genes are listed in the table.

Gene Symbol	Definition	Significance(p)
COMT	catechol-O-methyltransferase	0.00005797480452
PRL	prolactin	0.0001380405129
BDNF	brain derived neurotrophic factor	0.0001749323912
BDNF-AS	BDNF antisense RNA	0.0002309671043
DRD1	DISC1 scaffold protein	0.000379338441
CACNA1C	calcium voltage-gated channel subunit alpha1 C	0.0003799420456
SLC6A3	solute carrier family 6 member 3	0.0005368047278
CYP2D6	cytochrome P450 family 2 subfamily D member 6	0.0006313014603
SLC6A4	solute carrier family 6 member 4	0.0006889970894
HCRT	hypocretin neuropeptide precursor	0.0007320798757
APP	amyloid beta precursor protein	0.0007359766804

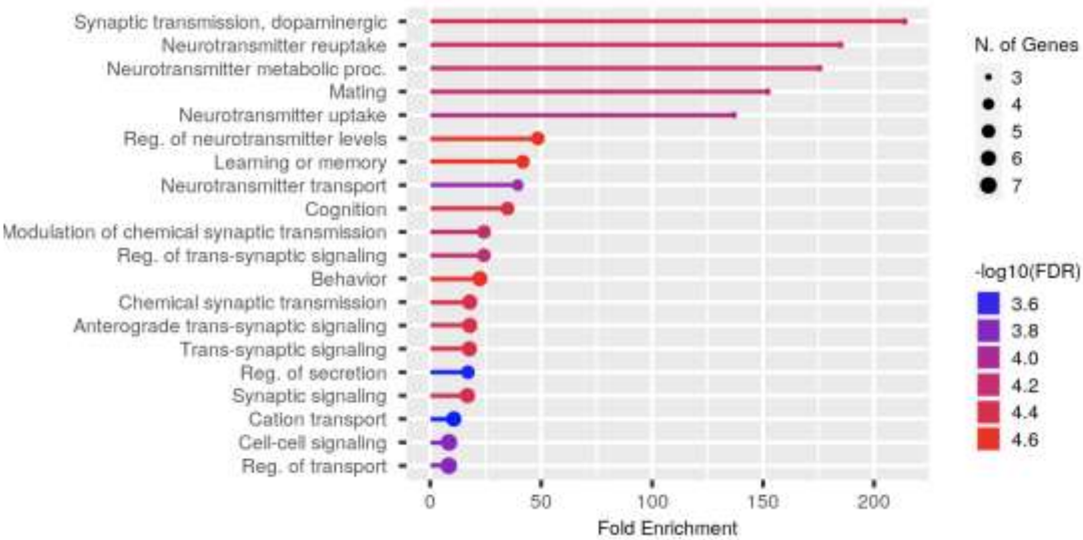

Figure 16: Gene Enrichment Results for" hypersomnia" and" Schizophrenia".

Most of the genes in the list are grouped into Neurotransmitter levels "cognitive ie learning or memory and behavior . The strongest enrichment was observed for Synaptic transmission ,dopaminergic processes.

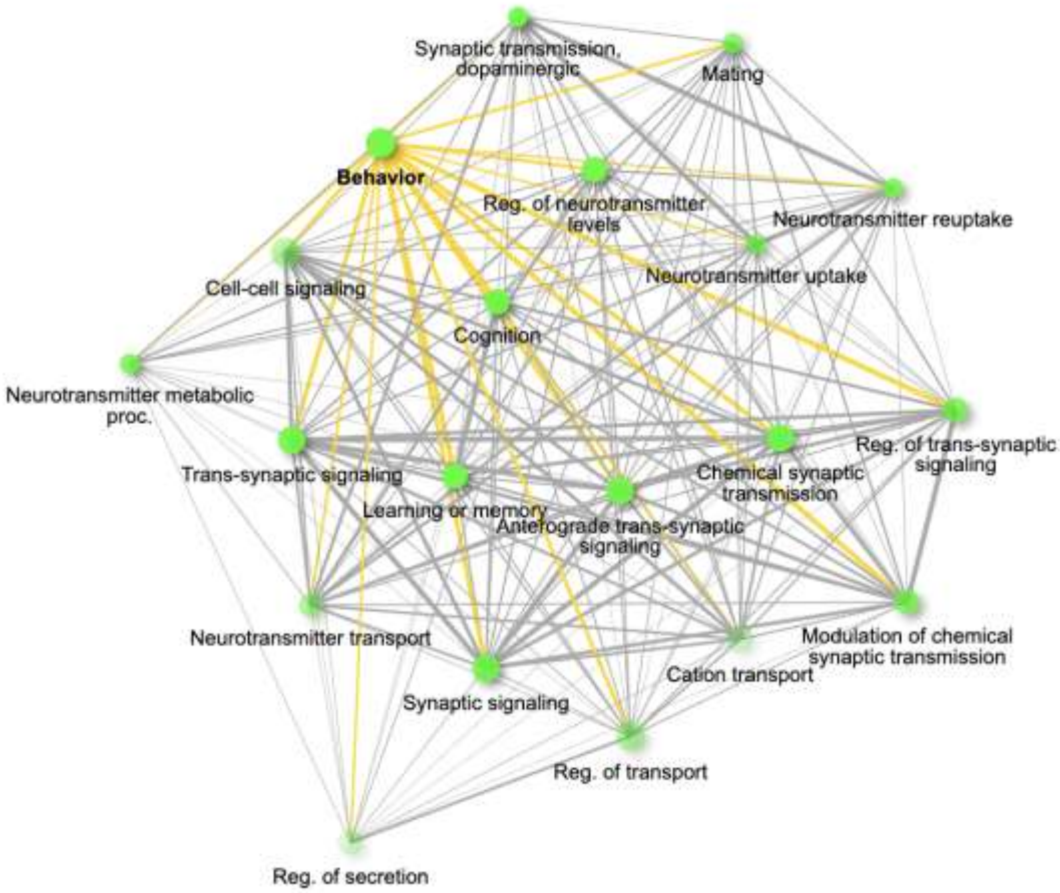

Figure 17: Gene Enrichment Network for "hypersomnia" and "Schizophrenia"

the nodes identified in Figure 16 Are shown with relation.

Table 10: Genes at the Intersection of "Hypersomnolence" and "Schizophrenia"

Gene Symbol	Definition	Significance (p)
PRL	prolactin	0.0001368365736
GRM2	glutamate metabotropic receptor 2	0.0003405555255
SLC6A3	solute carrier family 6 member 3	0.000521369118
APP	amyloid beta precursor protein	0.0007334559126

The most significantgenes are listed in the table.

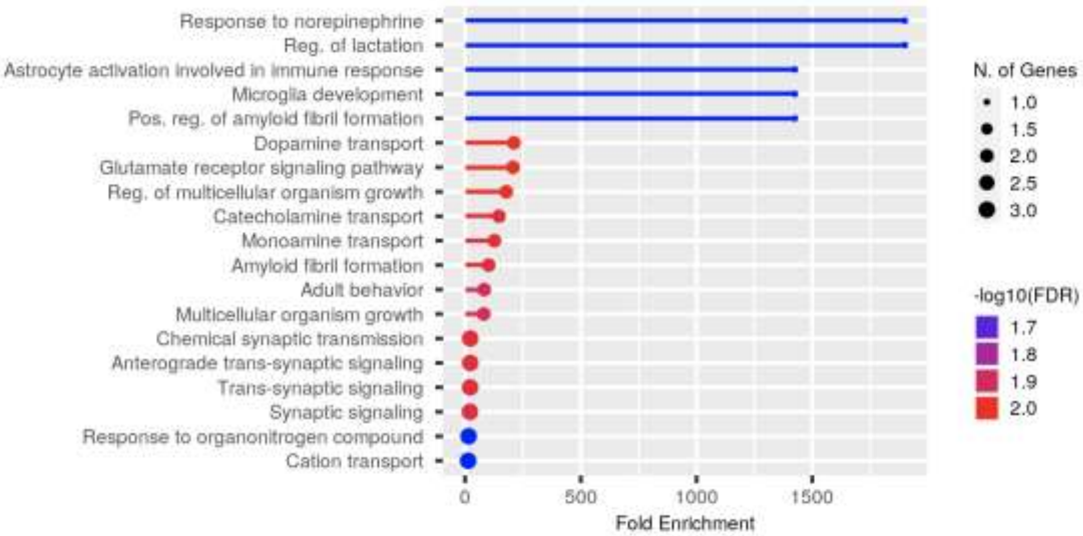

Figure 18: Gene Enrichment Results for" hypersomnolence and" Schizophrenia".

Most of the genes in the list are grouped into chemical synaptic transmission,anterograde trans-synaptic signaling ,trans -synaptic signalling . The strongest enrichment was observed for response to norepinephrine ,Reg of lacation .

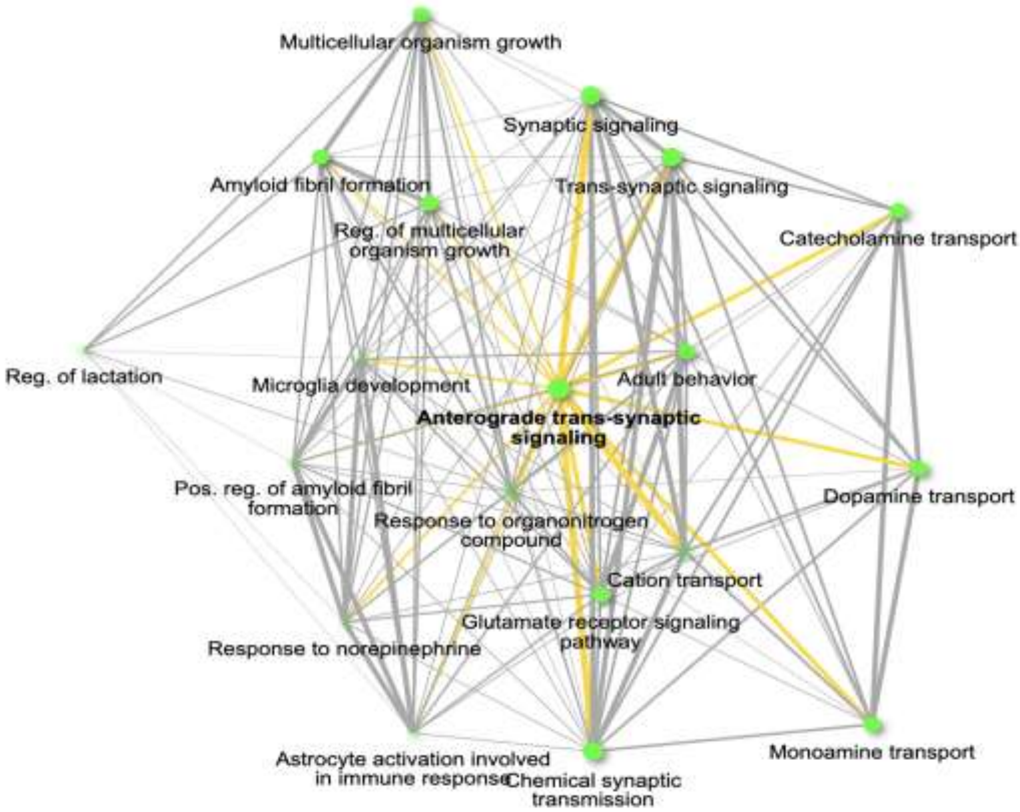

Figure 19: Gene Enrichment Network for "hypersomnolence" and "Schizophrenia"

.the nodes identified in Figure 18 Are shown with relation.

4.4.4 Other Sleep-related Symptoms and Schizophrenia

The symptoms that can be grouped under **others** were "Impaired Sleep", "Snoring" and "Nocturnal Myoclonus". The resulting lists were then saved in .xls format. The significance of these genes for further analysis was set at $p<0.001$. The results are given in Table 11,12 and 13. For nocturnal myoclonus, there was only one gene target, DRD2 (dopamine receptor D2).

Table 11: Genes at the Intersection of “Impaired sleep” and “Schizophrenia”

Gene Symbol	Definition	Significance (p)
BDNF	brain derived neurotrophic factor	0.0001716761647
HTR1A	5-hydroxytryptamine receptor 1A	0.0002205188866
BDNF-AS	BDNF antisense RNA	0.0002263448422
GRM2	glutamate metabotropic receptor 2	0.0003364803497
SLC6A3	solute carrier family 6 member 3	0.0005262014201
GRIN2B	glutamate ionotropic receptor NMDA type subunit 2B	0.0006052848979
SLC6A4	solute carrier family 6 member 4	0.0006746922095
APP	amyloid beta precursor protein	0.0007304666773
GRIN2A	glutamate ionotropic receptor NMDA type subunit 2A	0.000790842443

The most significant genes are listed in the table.

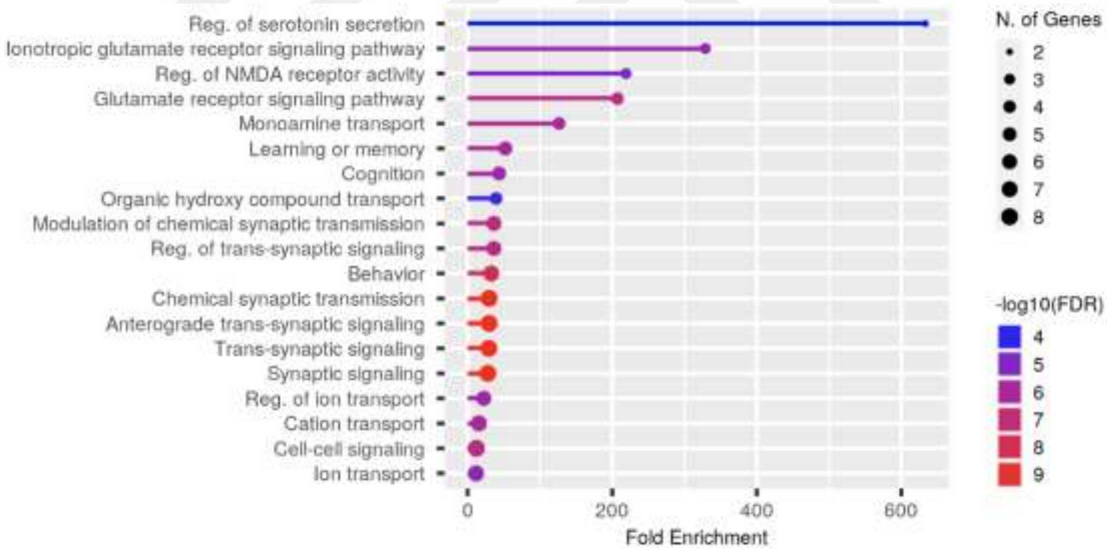

Figure 20: Gene Enrichment For "Imparired Sleep" And" And" Schizophrenia"

Most of the genes in the list are grouped into Chemical Synaptic transmission ,Synaptic signaling ,Anterograde trans -synaptic signaling   The strongest enrichment was observed for Reg.of serotonin secretion .

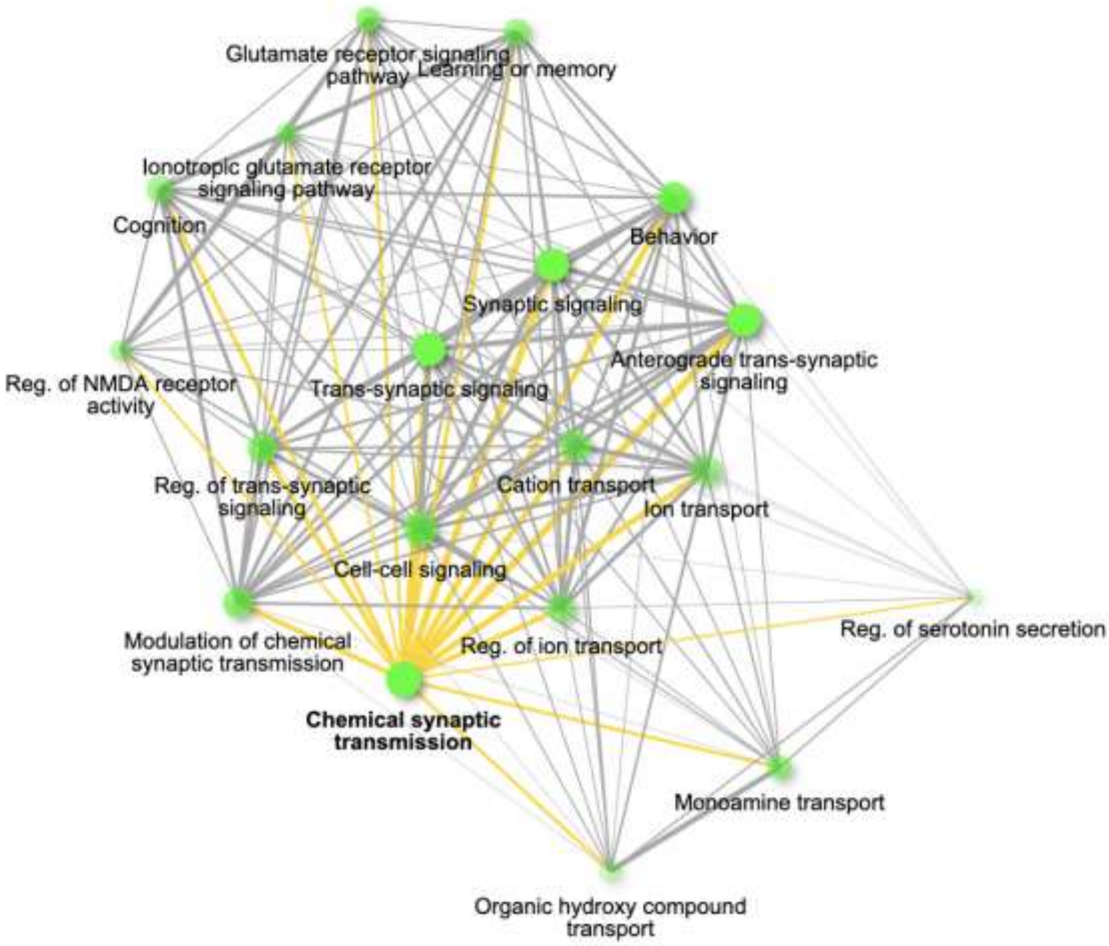

Figure 21: Gene Enrichment Network for "Impaired sleep" and "Schizophrenia"

the nodes identified in Figure 20 Are shown with relation.

Table 12: Genes at the Intersection of "Snoring" and "Schizophrenia"

Gene Symbol	Definition	Significance (p)
HTR2A	5-hydroxytryptamine receptor 2A	0.00006495425681
PRL	prolactin	0.0001447044199
HTR2C	5-hydroxytryptamine receptor 2C	0.0002152383435
HTR1A	5-hydroxytryptamine receptor 1A	0.0002323014373
CENPJ	centromere protein J	0.0005547582406
SLC6A4	solute carrier family 6 member 4	0.0007140054841
APP	amyloid beta precursor protein	0.000797253654

The most significant genes are listed in the table.

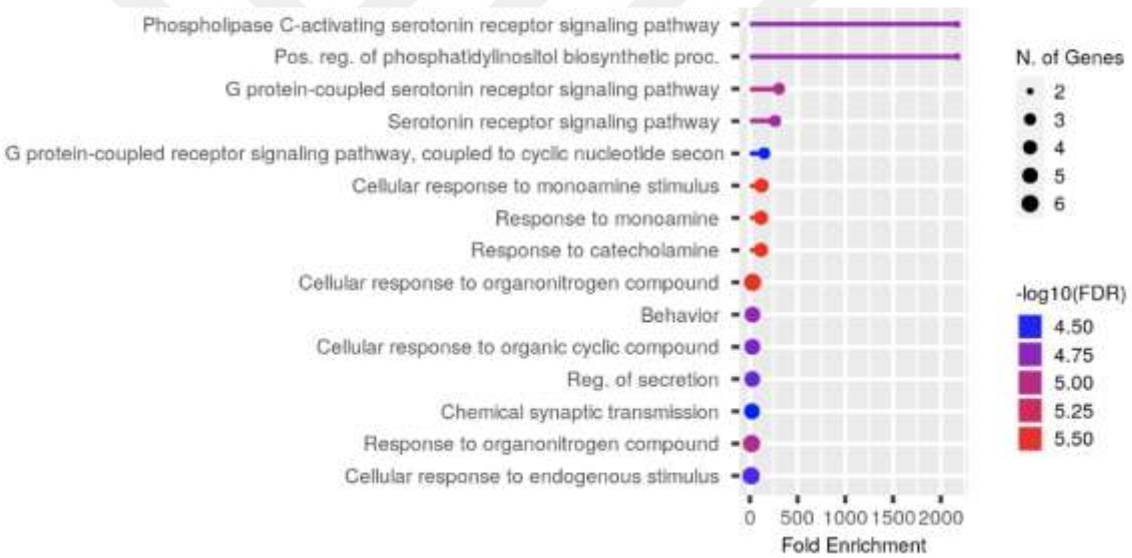

Figure 22: Gene Enrichment Results for " Snoring" and" Schizophrenia"

Most of the genes in the list are Cellular response to organonitrogen compound , Response to monoamine, Respones to The strongest enrichment was observed for phosophlipase C-activating serotonin receptor signaling pathway and Pos,reg phosphatidylinositol biosynthetic proc.

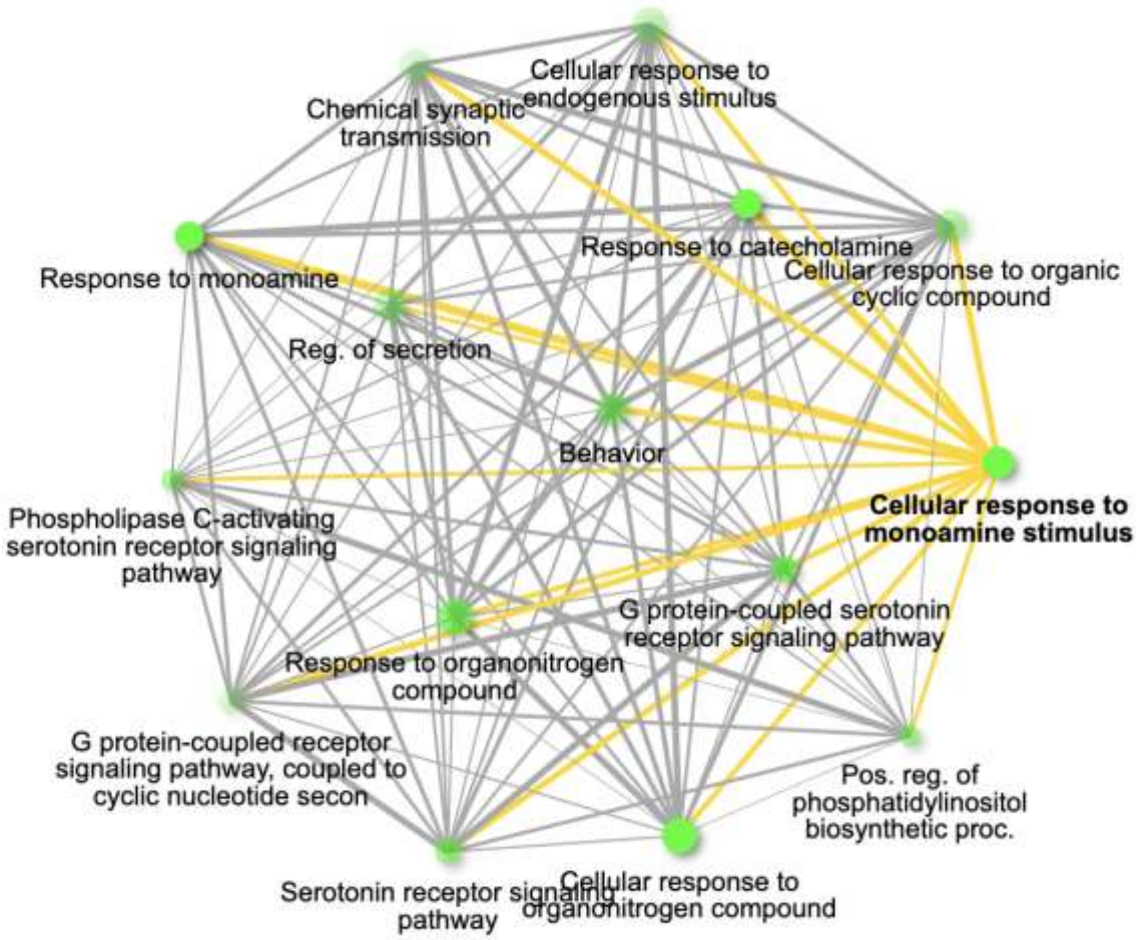

Figure 23: Gene Enrichment Network for "for "Snoring" and "Schizophrenia"

.the nodes identified in Figure 22 Are shown with relation.

4.4.5 Common Gene Targets for Symptom Groups

As the last step of analysis, the genes that are commonly targeted for insomnia and hypersomnia were evaluated. The results are given in Table 13 for insomnia-related symptoms and Table14 for hypersomnia-related symptoms.

Table 13: The most common genes related to insomnia (sleep difficulty ,sleeplessness) schizophrenia.

GENE SYMBOL	SLEEP DIFFICULTY	SLEEPLESSNESS
BDNF	0.0001757684416	0.0001860024572
BDNF-AS	0.0002319959002	0.0002442142393
COMT	0.00005959119891	0.00006478171231
DRD2	0.0000282638089	0.00003106282197
HTR2A	0.00006460440603	0.00006630788315
PRL	0.0001432831695	0.0001582235035
SKAP2	0.000197156472	0.0002189291088
CACNA1C	0.0003964459611	0.0004212786066

Table 14: The most common genes related to hypersomnia assoscited to schizophrenia.

GENE SYMBOL	HYPERSOMNIA /HYPERSOMNOLENCE	EXCESSIVE SOMNOLENCE
BDNF	0.0001749323912	0.0001762565087
BDNF-AS	0.0002309671043	0.0002326360095
COMT	0.00005797480452	0.00005816251608
HCRT	0.0007320798757	0.0003242021192
PRL	0.0001380405129	0.0001410706204
DRD1	0.000379338441	0.0003768968548
APP	0.0007334559126	0.0007199026814
SLC6A3	0.000521369118	0.0005406318702
SLC6A4	0.0006889970894	0.0007051475994
CYP2D6	0.0006313014603	0.0006874612048

4.6 Detailed Identification for the Target Genes and Molecular Processes in Humans

Through text-mining, the lists of genes that can be targeted for the sleep-related problems in schizophrenia were obtained. These genes were further analyzed for their actual relationship, e.g. changes in gene expression, polymorphisms. The survey was conducted on PubMed and Google Scholar with the formula

"Gene Symbol" AND "schizophrenia" AND "symptoms"

where the gene symbol and symptom was replaced by the target genes from the lists and the symptoms that were analyzed in detail. The genes that could be identified with detailed molecular information in relation to sleep-related symptoms in schizophrenia are given in Table 16. Some of the genes that displayed significant symptomatic relationship in schizophrenia through text-mining could not be identified with this method in the literature in relation to any of the symptoms. These genes were DISC1, DRD3, DRD4, HCRT, HTR1A, HTR6, NRG1, NRXN1, PVALB, SKAP2, CHRFAM7A, CHRNA4, CHRNA7, DRD1, GRIN1, GRM5, IGLON5.

Table 15: Genes sleep-related symptoms (insomnia, hypersomnia) in schizophrenia.

GENE SYMBOL	INSOMNIA	HYPERSOMNIA	REFERENCE
BDNF	Exposure to psychological stress leads to a decrease in BDNF levels in brain regions. Disruptions in sleep homeostasis lead to increased stress, and that might give an indirect relationship for BDNF and insomnia. There is no direct link in the literature.	-	Schmitt et al., 2016
COMT	-	Hypersomnia was genotyped for the Val158Met polymorphism (rs4680) in the COMT gene. The	Kim et al., 2017

		results showed higher scores for hypersomnia and lower scores for mental health-related quality of life.	
DRD2	DRD2IN polymorphism : Patients with the A1+ allele had higher higher subscale scores for various psychological disorders, such as depression and anxiety . There is no direct link in the literature.	-	Lawford et al., 2003
CACNA1C	CACNA1C rs11615998 is associated with HDRS (Core Depressive; Somatic; Psychotic-like; Insomnia). There is no direct link in the literature.	-	Calabrò et al., 2020
SLC6A4	LALA-genotype variation may increase the risk of insomnia.	-	Pallesen et al., 2019
CYP2D6	-	The occurrence of hypersomnia increased as the number of CYP2D6 mutant alleles increased.	Saruwatari et al., 2006
HTR2A	-	HTR2A polymorphism genotypes are linked to a higher risk of having poor-quality sleep.	Jiang et al., 2016
HTR2C	Rs1414334 has higher incidence of insomnia		Koller et al., 2021

Some of the genes that were identified in relation to sleep and schizophrenia did not emerge in the lists for sleep-related symptoms. The list of these genes and information on their role is given in Table 16

Dependent to our results these genes are not related to sleep disorders . so we looked for their function of them and utilizing the literature we notice that GRM3 and SLC6A9 play important roles in neurotransmitters in the central nervous system, and the PDE10A is related to neuropsychiatric disorders and the ZNF804A related to schizophrenia and the DTNBP1 This gene plays a role with other genes in adult neurogenesis and also neuroplasticity.

Table 16: Genes in relation to sleep and schizophrenia did not emerge in the lists for sleep-related symptoms.

Gene Symbol	**Function**	**Reference**
PDE10A	This gene has role in development of neuropsychiatric disorders my provide in sight in to mechanism by witch the gene can be linked to these disorders	MacMullen et al.,2017
GRM3	Is a major and important neurotransmitter in the central nervous brain function	Gene-NCBI n.d.
SLC6A9	Central nervous neurotransmitter	Gene-NCBI n.d.
ZNF804	One of the most potential genes	Zhang et al.,2016
DTNBP1	This gene play role in adult with other genes in neurogenesis and neuroplasticity	Lestrat et al.,2009

5. DISCUSSION

In this thesis, the main question was whether the relationship between schizophrenia and sleep-related symptoms can be identified through genetic etiology or not. Text-mining enables us to scan the accumulated scientific literature and to find hidden or not so direct relationships in these findings. Therefore, the main method for the thesis was text-mining through a simple and easily accessable algorithm, CoreMine Medical.

Our results point to three important conclusions. First, there is a gap in the literature on the direct relationship of genes and sleep-related symptoms. Through text-mining, genes that are related to sleep problems in schizophrenia were identified specifically for insomnia and hypersomnia (Table 14 and 15). However, the scientific literature do not actually have a direct relationship for most of these genes. Some of the genes that displayed significant symptomatic relationship in schizophrenia through text-mining could not be identified with this method in the literature in relation to any of the symptoms. These genes were DISC1, DRD3, DRD4, HCRT, HTR1A, HTR6, NRG1, NRXN1, PVALB, SKAP2, CHRFAM7A, CHRNA4, CHRNA7, DRD1, GRIN1, GRM5, IGLON5. Even though we have information on genetic links in schizophrenia and /or sleep-related problems, it was clear that there are very few studies that focused on identifying the link between genes and symptoms. For example, one of the most common target genes from our findings, HCRT, codes for the preproorexin, which is converted to orexin A and orexin B. Both these neurotransmitters are crucial in proper sleep regulation. Orexin levels are known to be altered in schizophrenia patients (Deutch & Bubser, 2007). But these changes were not correlated with the sleep-related symptoms that emerge in these patients. It is important to identify these direct relationships, i.e. to design future personalized therapies targeting sleep-related problems in schizophrenia patients.

Secondly, some of the genes that were identified in relation to sleep and schizophrenia did not emerge in the lists for sleep-related symptoms. These genes (PDE10A, GRM3, SLC6A9, ZNF804). should be investigated further in terms of sleep problems.

Thirdly, the simplicity of the text-mining method we utilized shows us that there is indeed important and valuable information hidden in the scientific literature. These relationships can also be further addressed with more extensive and advanced text-mining algorithms.

6. CONCLUSION AND FUTURE DIRECTIONS

The fundamental concern of this thesis was whether or not there was a genetic basis for the association between sleep-related symptoms and schizophrenia. We may search the body of scientific literature using text mining to look for obscure or indirect correlations between these discoveries. Thus, text mining using CoreMine Medical, a straightforward and accessible technique, served as the thesis' primary methodology.

The direct connection between genes and sleep-related disorders is not well covered in the literature. Genetic factors connected to insomnia and hypersomnia in schizophrenia have been discovered by text-mining.It was evident that there are relatively few research that focused on determining the relationship between genes and symptoms, despite the fact that we have knowledge of genetic links in schizophrenia and/or sleep-related issues. The lists for sleep-related symptoms did not include some of the genes that were linked to schizophrenia and sleep. Further research on these genes (PDE10A, GRM3, SLC6A9, and ZNF804) should be done in relation to sleep issues.The identified genes can we used for personalized medicine It is a type of medicine used to diagnose, plan treatment, or discover how successful treatment is . Can be used to design genetic screening kits .The main advantage is that early detection may prevent more severe forms of a disease or prevent a couple from having a sick child.

We need Further research. on study the development and use of gene expression techniques describe the most widely used methods for analyzing the levels of RNA in tissues and cells

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APPENDIX

Appx. 1.

Appx. 2. Curriculum Vitae

CURRİCULUM VİTAE

Name Surname :
Birth Place and Date :
Foreign Language/s :
Phone :
E-mail :

Education:
High School :
Bachelor's Degree :
Master Degree :

Work/Business Experience :